AALTO UNIVERSITY
SCHOOL OF ELECTRICAL ENGINEERING
Department of Electronics
Bioadaptive Technology

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Market study for nebulization with invasive mechanical ventilation

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ABSTRACT OF THE
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Aerosol therapy delivers the drug to the body via airways by taking advantages of the inhaled route for the treatment of respiratory diseases and non-pulmonary diseases. Recent development of aerosol delivery device technologies and advantages of inhaled route present a unique opportunity to exploit market opportunities of new aerosol device technologies with mechanical ventilation. The case company of this study has developed a new solution for nebulization with invasive mechanical ventilation, and this study discusses the current market situation for this solution.

The research methods used in this study is a combination of literature review and case study. The literature review identifies the main nebulization therapy techniques and main technical or physical factors affecting the nebulization therapy for patients with invasive mechanical ventilation. Based on the interviews of the case study current practices and customer needs in nebulization with invasive mechanical ventilation are recognized.

The ability of current practices to meet these customer needs is analyzed, and the solution of the case company is evaluated compared to current practices. As a part of this analysis, an opportunity and issue analysis for features of the case company's solution is performed.

As an outcome, major competitive advantages of the case company's solution are recognized. These are the position free operation of the nebulizer unit and the possibility for increased delivery as a result of the new placement of the nebulizer. In addition, the case company's solution provides benefits also in other features that ease the workflow of nebulization treatment.

Keywords: aerosol therapy, nebulization, nebulizer, inhalation drug delivery

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Inhalaatiolääkinnässä lääke toimitetaan elimistöön esimerkiksi lääkesumutteena käyttäen hengitysteitä annostelureittinä. Tämän annostelureitin edut yhdistettynä viimeaikaiseen lääkesumuttimien tekniseen kehitykseen ovat luoneet erityisen markkinamahdollisuuden uusille mekaanisen ventilaation yhteydessä käytettäville inhalaatiolääkintätekniikoille. Tämän tutkimuksen tavoitteena on tarkastella markkinatilannetta tapausyrityksen kehittämälle invasiivisen ventilaation yhteydessä käytettävälle inhalaatiolääkintäratkaisulle.

Työssä käyetty tutkimusmenetelmä on yhdistelmä kirjallisuuskatsausta ja tapaustutkimusta. Kirjallisuuskatsauksen avulla luodaan käsitys inhalaatiolääkintätekniikoista sekä teknisistä ja fysikaalisista tekijöistä, jotka vaikuttavat inhalaatiolääkintään invasiivisen mekaanisen ventilaation yhteydessä. Tapaustutkimuksessa tehtyjen haastatteluiden avulla tunnistetaan nykyiset inhalaatiolääkintäkäytännöt ja asiakastarpeet invasiivisen mekaanisen ventilaation yhteydessä suoritetulle lääkinnälle.

Työssä arvioidaan nykyisten käytäntöjen kykyä täyttää tunnistetut asiakastarpeet sekä vertaillaan tapausyrityksen ratkaisua nykyisiin käytäntöihin. Osana tätä arviointia suoritetaan mahdollisuus- ja haasteanalyysi tarkastellulle ratkaisulle.

Lopputuloksena tunnistetaan tapausyrityksen ratkaisun kilpailuedut. Näitä ovat lääkesumuttimen toimiminen eri asennoissa sekä uuden sijoittelun mahdollisesti luoma parempi hyötysuhde. Lisäksi tämä ratkaisu yksinkertaistaa mekaanisen ventilaation yhteydessä suoritettavan inhalaatiolääkinnän työvaiheita.

Keywords: nebulisaatio, nebulisaattori, lääkesumutin, inhalaatiolääkintäääkintä

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PART I: INTRODUCTION

1. Introduction

Worldwide hundreds of millions of people suffer from chronic respiratory diseases. These are diseases of airways and other structures of the lungs. Some of the most common are asthma, chronic obstructive pulmonary disease, respiratory allergies, occupational lung diseases and pulmonary hypertension. According to World Health Organization approximately 300 million people have asthma, 210 million people have chronic obstructive pulmonary disease, and millions of others have other respiratory diseases (WHO, 2012). This number of people suffering from chronic respiratory disorders is constantly growing. The burden of chronic respiratory diseases has become a socioeconomic problem that cannot be addressed by the public health sector alone. To tackle this challenge there is collaboration between many sectors of society.

High interest of these several parties, development of modern technology along with increasing understanding of human pulmonary physiology has improved systems to treat various respiratory diseases. One increased method for treatment of respiratory diseases is aerosol therapy, which refers to the delivery of drugs to the body via airways by delivering it in an aerosolized form. Aerosol therapy makes use of the inherent advantages of the inhaled route of drug administration for the treatment of respiratory diseases and also non-pulmonary diseases. According to Dhand (2008) a key advantage of inhaled route is that it enables delivery of the drug to its site of action for a localized effect, which leads to a rapid clinical response with minimal systemic side effects. This advantage is even emphasized in patients with severe or acute respiratory disorders.

Patients with a severe or an acute respiratory disorder might require ventilation support. In addition, the breathing rate and depth of patients with a respiratory failure require increasing, either by reversing the cause of a respiratory failure or by artificial ventilation support. Mechanical ventilation is a method to mechanically assist or replace spontaneous breathing. European Respiratory Society (ERS, 2001) recommends administrating aerosols for patients receiving mechanical ventilation, in order to reduce the airway resistance and to reduce the risk of ventilator associated pneumonia. For this reason, mechanically ventilated patients present a unique opportunity to exploit the inhaled route for drug delivery.

Progress has recently been made in several areas related to the aerosol delivery of drugs for mechanically ventilated patients. Especially, there has been progress in understanding the various factors that influence aerosol delivery and deposition in ventilator-supported patients, and in the development of new technologies for aerosol generation. At the moment virtually all drug therapies, except for treatment of airway diseases, are given systemically by injection or infusion. This is because the inefficiency of previous techniques for aerosol therapy. Keeping in view the

development of aerosol delivery techniques, it appears that aerosol therapy for mechanically ventilated patients is now becoming a standard of care.

Nebulization is aerosol delivery method with long tradition in treatment of airway diseases, where liquid medication is delivered to the lung as a mist via airways. Traditional nebulizers have used gas flow as a driving force, when the more recent techniques utilize the high ultrasonic vibration. This has increased the efficiency of nebulizers, and made them potential technique for aerosol delivery of ventilated patients.

Nowadays, also the growing market opportunity for aerosol therapy has increased interests in several companies to develop either drugs or delivery systems for aerosol therapy. The case company of this study is one of the global leaders in the healthcare market, and is developing a new technique for nebulization with ventilated patients. To succeed in this growing and competitive market, the case company needs more understanding of the situation in this targeted market.

Thus, the need to understand markets forms the main research problem of this study. This main research problem is:

- What is the current market situation for the nebulization with invasive mechanical ventilation?

Three research objectives to be answered can be generated from this research problem:

- Identifying the main nebulization therapy techniques and main technical or physical factors affecting the nebulization therapy for patients with invasive mechanical ventilation.
- Identifying current practices of nebulization for patients with invasive mechanical ventilation.
- Defining the customer needs for patients with invasive mechanical ventilation, and analyze how current practices can meet these demands.

Even though economic factors have an impact on the adapting of new technology, these factors are not in the scope of this study. The scope of this study is in the features of nebulizers and current practices in-hospital. In addition, because of the scope, this study does not evaluate the situation of other aerosol therapy technologies or situation outside hospitals.

According to Aaker et al. (2007) effective marketing strategies are built on in-depth understanding of the market environment of the business and the specific characteristics of the market. For this reason, this study concentrates on understanding the current market situation for the nebulization solution of the case company. The scope of this study is in the market situation analysis and on its effects on strategy development, but not in the marketing strategy development for the nebulization solution of the case company.

This study has been divided into four parts that each consists of one or several chapters. The study starts with an introductory part that forms an overview of the topic and describes the research problem and the scope of the thesis. The second part is the literature study that discusses the theoretical background and context of aerosol therapy and aerosol therapy with mechanical ventilation. Within the part the main nebulization therapy techniques and main factors affecting the nebulization therapy for ventilated patients are discussed. In addition the theoretical framework for market study is discussed in the second chapter.

The third part consists of the market study. First, the research methods and tools are described. Then results from the market research are presented. After presenting results, they are analyzed with the theoretical findings and other findings from the market research. Finally at the end of the study, the fourth part includes the discussion and results of the study.

PART II: LITERATURE STUDY

2. Market Study

This chapter describes the concept of the market study, its objectives and relation to strategy. Firstly, this chapter forms a definition for market study and presents the methods for information gathering in market study. Finally, the elements used in this work to draw conclusions from the information are presented.

2.1. Market study concept

Market study is an organized effort to gather information about markets of specific topic. The results of the market study describe the current situation. For this reason, it can be seen as a part of market situation analysis. Market situation analysis is a step of the marketing planning process presented in Figure 2-1. According to Aaker et al. (2007) the purpose of the marketing situation analysis is to obtain adequate background information of various elements, which affect the marketing operations of a business. This analysis of the current situation, serves as the basis for identifying opportunities to satisfy unfulfilled customer needs. At the end, the situation analysis should yield knowledge of the markets and future prospects. In addition, marketing planning process is a never-ending process, and the evaluation of past strategic decisions serves as an input to the situation assessment.

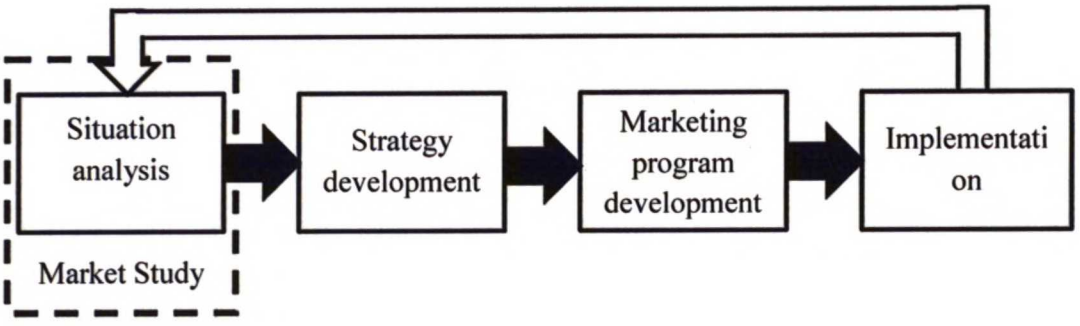

Figure 2-1. Marketing planning process. Modified from (Aaker, et al., 2007).

2.2. Marketing information

Kotler (1997) suggests that the marketing information can be received from multiple sources such as internal company records, from marketing intelligence or from marketing research. Usually majority of this information is already possessed within the company, but people fail to share the information. For this reason there is a need to use

different methods to gather this information, in order to benefit from it in marketing situation analysis.

Internal records consist of information gathered from sources within a company. Usual sources in a company are accounting department, the manufacturing, the sales force, the customer service, and the research department. Information from internal records is usually quicker and cheaper than information from other sources Anyhow, gathering information from internal records is not without problems, because internal information is usually intended for other purposes. For this reason, the internal information usually requires further processing to be used. (Kotler, et al., 1996)

Kotler (1997) classifies marketing intelligence as knowledge about the current marketing environment. A part of this information already exists within the company, but in addition the marketing intelligence can be gathered from distributors, retailers, and other intermediaries. Also, companies can always purchase this information from outside suppliers like research firms.

Marketing research is a process to gather information relevant to a specific marketing situation facing the company. Five steps that Kotler (1997) recognizes in effective marketing research are presented in Figure 2-2. This process starts from defining the research objectives and plan, followed by collection, analysis, and reporting of data and findings.

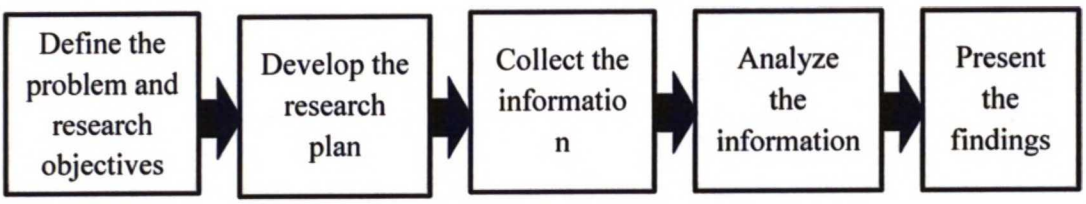

Figure 2-2. The marketing research process. (Kotler, 1997)

2.3. Customer needs and competitive evaluation

Markets consist mainly of buyers, who may differ in their desires, resources, locations, buying attitudes and buying practices. According to Kotler et al. (1996) dividing these buyers into smaller groups with similar behavior is called segmentation. Identifying the possible market segments allows seeing the market opportunities and comparing them in order to finally select which segments are worth of focusing on. For efficient segmentation and evaluation it is required to not only know the characteristics of customers, but also know the benefits that customers look for.

Although marketing is about meeting needs profitably, understanding customer demands is not always a simple task. Some customers have needs of which they are not fully aware of, or they cannot articulate these needs. For this reason, Kotler et al. (1996) suggests that answering only to stated customer needs may shortchange the customer.

One method to recognize the customer needs is to clarify the challenges that customers are currently facing, and evaluate the ability to solve these.

In a process of assessing the factors which are particularly important to the customer, it is possible to utilize methods from surveys to focused group interviews. With these factors the customer needs and competitive evaluation can be combined with competitor array, presented in Figure 2-3. In competitor array the customer needs are recognized and displayed in two-dimensional matrix with competitors. Then the competitors are rated inside each success factors, and the overall strength of each competitor relative to each other is possible to achieve. It is also possible to have unique value for each of the success factors, instead of valuing them equally. In this case, the importance of each success factor is ranked, and then the weighted assessment is achieved. (McGonagle & Vella, 2012)

Key Success Factors	**Competitor #1**	**Competitor #2**	**Competitor #3**	**Competitor #4**
	Rating	**Rating**	**Rating**	**Rating**
Success Factor #1				
Success Factor #2				
Success Factor #3				
Success Factor #4				

Figure 2-3. Competitor array for competitor evaluation. Modified from (McGonagle & Vella, 2012).

2.4. Opportunity and issue analysis

Market where companies act is usually composed of many elements. To deal with these elements the companies have to form cause-and-effect type of relationships between them. Based on the origin of the elements, Kotler (1997) divides these into two categories: external factors and internal factors.

The first category implies the external environment which contains all changes that take place outside the company's boundary and to which company has little impact. This external analysis focuses on characteristics that could produce opportunities as well as threats relative to competitive solutions. Kotler & Amrstrong (2010) describes an opportunity as an area of buyer needs, where a company can perform profitably. In comparison, threats can prevent the profitable performance of the company.

The second category has to do with internal factors and variables that can be controlled within an organization. If results from one of these factors are satisfactory, then it will reflect the strength of the company with this factor. While if the results are poor and

unsatisfactory, then it will prove that some factors are weaknesses of the company. Kotler (1997) calls this evaluation of company's strengths, weaknesses, opportunities and threats as SWOT analysis. SWOT analysis can be presented in matrix form, as in Figure 2-4.

	Helpful to achieving the objective	Harmful to achieving the objective
Internal Origin	**Strengths**	**Weaknesses**
External Origin	**Opportunities**	**Threats**

Figure 2-4. SWOT matrix for opportunity and issue analysis.

Kotler (1997) suggest that only factors relating to success are needed to list in the final SWOT matrix. Reason for this is that a too long list causes a lack of focus and an inability to discriminate what is important. After strengths, weaknesses, opportunities and threats are gathered the company can analyze all these aspects together and draw conclusion for their strategy development. Kotler & Armstrong (2010) suggest that the best result is achieved by optimizing strengths and minimizing weaknesses to meet opportunities and avoid threats.

3. Aerosol therapy

Hasan (2010) classifies an aerosol as suspension of solid or liquid particles in a gas. When the particles in this suspension are in solid form the aerosol is referred to as dust, and when the particles are in liquid form the aerosol is referred to as spray. The particles in dust are generally irregular, on the contrary to particles in spray, which tend to be spherical owing to forces of surface tension. Treatment of the respiratory system with aerosol is referred to as aerosol therapy. In the beginning of this chapter, the human respiratory system is presented. After that, principles of aerosol therapy and the devices used for aerosol therapy are presented.

3.1. Human respiratory system

The human respiratory system is a complicated organ, which performs the exchange of gases between the atmospheric air and the human body. In this process carbon dioxide from the body is released and replaced with oxygen, which is transported from the lungs to body cells by the cardiovascular system. The human respiratory system, presented in Figure 3-1, consists of the nose, pharynx, larynx, trachea, bronchi and lungs. (Tortora & Derrickson, 2009)

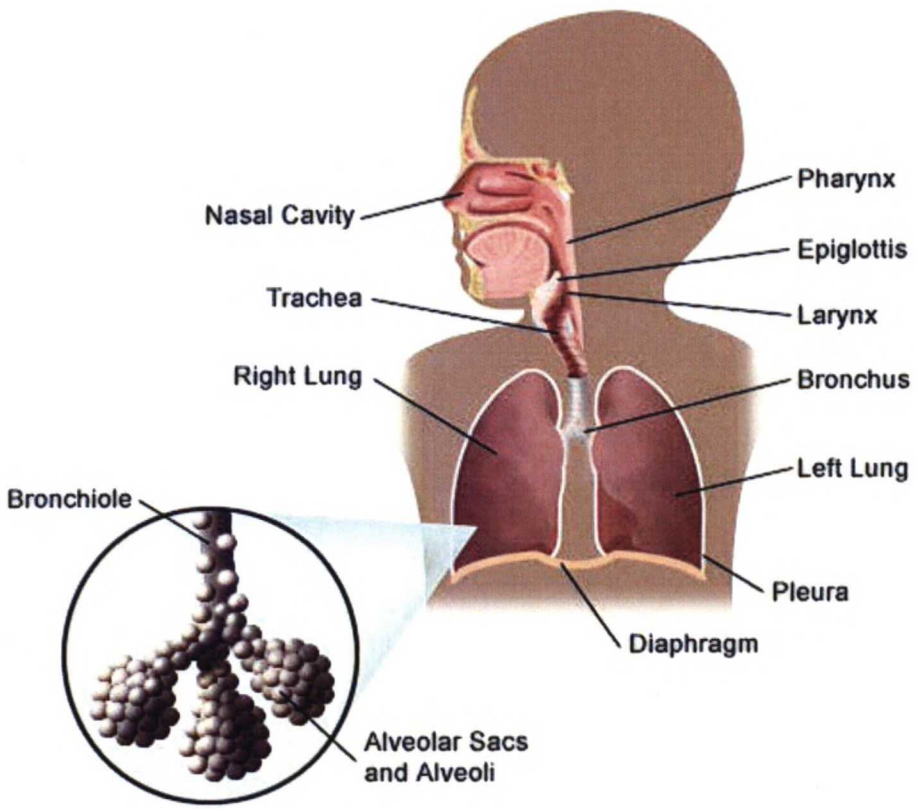

Figure 3-1. Presentation of the human respiratory organs. (Hospital, 2012)

The function of the nose is to work as a humidifier and a filter for inhaled gases. The pharynx, also referred to as a throat, works as a passageway for inhaled and exhaled gases. The larynx, commonly called the voice box, is located in the neck and it connects the pharynx to the trachea. The trachea is tubular passageway for air to the lungs and in the end trachea divides into bronchi. Bronchi divide to two new bronchioles with smaller diameters and shorter lengths. These bronchioles keep repeatedly branching until they subdivide into alveolar ducts and alveolar sacs, where gas exchange takes place. (Weibel, 1991)

The respiratory system can be classified either by structure or by function. If it is classified by structure, larynx works as a divider between upper- and lower respiratory system. The respiratory system can also be divided into the conducting zone and the respiratory zone by function. Then the conducting zone consists of series of interconnecting cavities and tubes from the nose to the terminal bronchiole. The gas exchange occurs in the respiratory zone, which consist of respiratory bronchiole and alveoli. (Tortora & Derrickson, 2009)

From the trachea the airway repeatedly branches and each time the number of branches is doubled and cross sectional area is exponentially increased. As a result from that, the human lungs contain 300-600 million alveoli (Gaultier, 1999) and these compose the seventy square meter surface area (Tortora & Derrickson, 2009), where gas exchange occurs. The physiology and the anatomy of the lungs are age-related, when the total lung capacity is weight related. Total lung capacity, TLC, measures the total volume of air in the lungs after a maximal inspiration. According to Sharma et al. (2011) an adult's lungs have a total capacity of 80-85 ml per kilogram, when the neonates' lungs have only 55-70 ml per kilogram.

The reduced lung capacity is result of several factors. Firstly, the smaller pharynx of younger patients reduces the amount of air reaching the airways. Secondly, the mean airway diameter differs 200-300% (Hislop & Haworth, 1989) between birth and adulthood. Finally, according to Sharma et al. (2011) the amount of alveoli at birth is estimated to be 20-150 million, compared to 300-600 million alveoli that is present in developed lungs. The quantity of alveoli is not usually increasing after the age from five to six, but alveoli still continue to increase in size.

Because the air of the environment can contain pathogens or toxic gases, the inspired gases are exposed to three different defense mechanisms. Nicod (1999) classifies these to mechanical defense mechanisms (air filtration, cough, sneezing, and mucociliary clearance), chemical defense mechanisms (antioxidants, antiproteases and surfactant lipids), and immunological defense mechanisms. The mechanical defense mechanism can be considered as a filter that removes particles from the inspired air. This defense mechanism does not only limit the quantity of inhaled particles but also the size of these particles. (Plopper, 1996)

3.2. Respiratory mechanics

Ventilation refers to inhalation and exhalation of air between the atmosphere and the lungs, and it is also called breathing. In humans ventilation involves movement of the chest wall to produce a pressure gradient that will permit flow and movement of gas. The pressure differences generate air flow to or from the lungs. Inhalation is the flow of air from the external environment through airways into the lungs. Inhalation begins with the onset of contraction of the diaphragm, and is an active phase, when exhalation is a passive phase, where the air moves out of the lungs. (Tortora & Derrickson, 2009)

Respiration rate, RR, is the number of breaths taken within a given time, typically sixty seconds. The volume of one breath is called the Tidal Volume, TV, while the volume of air breathed during one minute is the minute volume, MV. During normal expiration not all air is exhaled. The volume of air remaining in the lungs after a normal expiration is called functional residual capacity, FRC. Vital capacity, VC, describes the maximal volume of air that can be exhaled after a maximal inspiration. (Tortora & Derrickson, 2009)

During normal breathing the whole tidal volume does not reach the respiratory zone. According to Tortora & Derrickson (2009) in a typical adult, thirty percent of the tidal volume remains in the conducting airways and only seventy percent of the tidal volume leaves the lungs. The thirty percent remaining in the conducting airways is referred to as an anatomical dead space. In adults the volume of that space equals approximately to the body weight in kilograms multiplied by 2.2 (Datex-Ohmeda, 2007). Thus, for 70 kg person, this is 150 ml of the total volume of one breath which is 500-700 ml.

During the development of the lungs the lung capacities and therefore the tidal volume are limited. For this reason, the increase in minute volume is achieved by high respiratory rate. All in all, the pulmonary functions of undeveloped and developed lungs differ dramatically and are presented in Table 3-1. After the development of the lungs is completed, the pulmonary functions are more weight related than age related. (Sharma, et al., 2011)

Table 3-1. Normal pulmonary functions of neonates and adults. (Sharma, et al., 2011)

	Neonatal	Adult
Total lung capacity (ml/kg)	55-70	80-85
Tidal volume (ml/kg)	5-7	7
Functional residual capacity (ml/kg)	27-30	30
Vital capacity (ml/kg)	35-40	60
Respiratory rate (breaths/min)	30-50	12-16
Alveolar ventilation (ml/kg/min)	100-150	60

3.3. Principles of aerosol therapy

Shaikh et al. (2010) reports how aerosols have been used medicinally for thousands of years and over the decade certain drugs have been sold in compositions suitable for pulmonary delivery. When the aerosol is delivered by inhalation it is called inhalation therapy. Inhalation therapy is used to describe a variety of treatment techniques targeting different parts of the respiratory system. When the drug is delivered in an aerosolized form it is referred to as aerosol therapy.

Aerosol therapy provides a possibility to deliver a high local concentration of the drug directly to the epithelium tissue in the trachea-bronchial or in alveoli. This direct delivery to the target site provides several additional benefits. Firstly, targeted delivery enables the rapid onset of the action in the target site compared to other modes of delivery. Secondly, Dhand (2004) reports that a similar therapeutic effect can be achieved with a smaller quantity of the same drug with aerosol therapy than with systemic administration. Finally, a smaller quantity and the delivery to the site of action limit the systemic absorption of the drug and minimize adverse effects. (Khilnani & Banga, 2008)

Besides the targeted delivery to the site of action, aerosol therapy can exploit the large surface area and minimal diffusion distance of the respiratory tract to deliver the drug to the systemic circulation. Due to these advantages, Daniher & Zhu (2008) states that aerosol therapy represents a valuable mean for treatment of several diseases. However, according to Dolovich et al. (2000) the most common diseases treated with inhalation therapy are respiratory disorders.

3.4. Mechanisms of the particle deposition in the lungs

The behavior of aerosol in airways is dependent on the particles it consists. These particles can vary in size and density. Both of these have an effect to the behavior, because particles similar in size and difference in density behave differently in the airways. For this reason, usually the particle size or droplet size of aerosol does not refer to the actual size but to a variable known as mass median aerosol diameter, MMAD. Mass median aerosol diameter expresses the deposition qualities of the particles within the airways, and particles with similar MMAD behave similarly.

The mass median aerosol diameter is computed based on the sedimentation of particles. When a particle starts to fall its velocity increases and with an increasing velocity the resistance increases. At a certain point the resistance does not permit the particle to fall any faster and a settling velocity is reached. Depending upon the settling velocity of a particle, its mass median aerosol diameter is computed. This mass median aerosol diameter may differ from the actual diameter. (Hasan, 2010)

Usually in aerosol therapy, the particle size refers to the mass median diameter. This size has an impact on aerosol therapy for two reasons. Firstly, not particles of all sizes can be inhaled, because of the mechanical defense mechanism. Secondly, the size of particles determines its behavior within airways.

Particles can be deposited in the respiratory tract by several mechanisms. The most common mechanisms are inertial impaction, sedimentation, and diffusion. Certain deposition mechanisms are dominant in different zones of the lungs, as shown in Figure 3-2. Deposition mechanisms are dependent on particle size and change of airflow rate, which keeps to decrease when moving further of the respiratory tract due to increase of the cross sectional area of airways. (Darquenne, 2006)

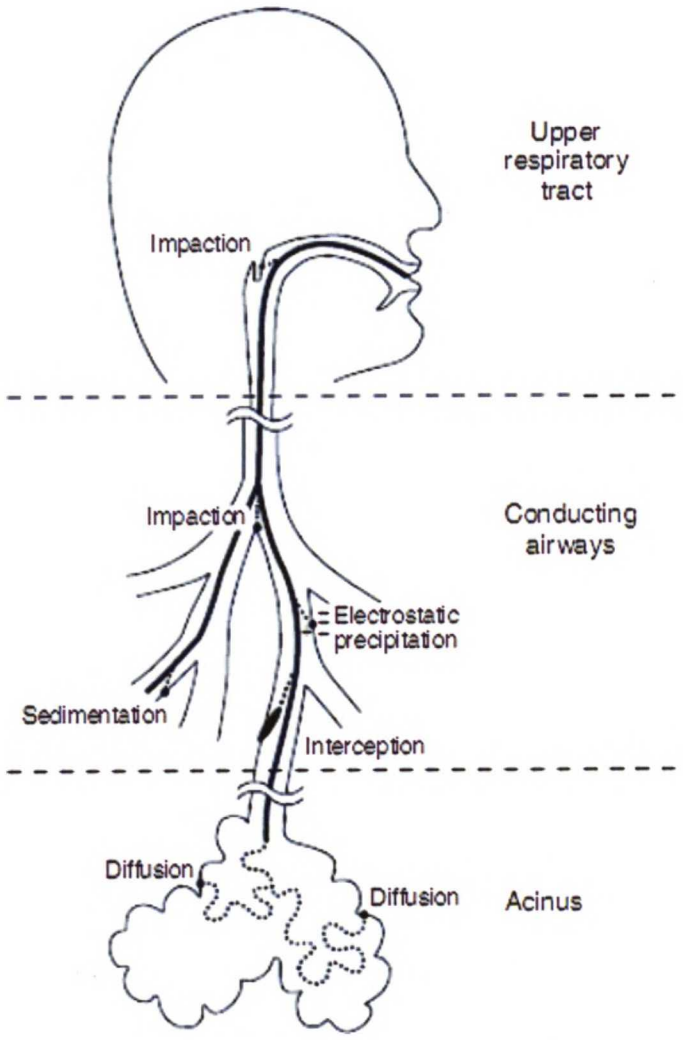

Figure 3-2. Dominant deposition mechanisms of inhaled particles presented in the zones of the respiratory tract. (Darquenne, 2006)

Inhaled particles traveling in airways follow the complex path of airflow. Changes in the rate of airflow may cause particles to deviate from their initial path and to eventually impact on airway walls. This deposition mechanism is referred to as inertial impaction. According to Schulz et al. (2000) inertial impaction occurs predominantly in the upper respiratory tract and in the conducting airways, where the airflow velocity is high and rapid changes in airflow direction occur. The deviation of the particle from the air streamline is greater for particles with a larger size. Generally, particles with size from three micrometers can be deposited by inertial impaction, which is the primary mechanism for particles larger than five micrometers. (Darquenne, 2006)

Sedimentation refers to the settling of particles under the action of gravity. Sedimentation occurs when the gravitational force equals the opposing viscous resistive forces of the air. The probability of sedimentation increases with increasing particle size

and density. Sedimentation is most likely for particles with a diameter from half to two micrometers. Although, deposition by gravitational sedimentation can also occur in the upper respiratory tract, it is dominant deposition method in small airways and alveoli. (Darquenne, 2006)

Deposition by impaction or sedimentation increases when the particle size increases. In comparison, according to Darquenne (2006) the deposition by Brownian diffusion increases with decreasing particle size and becomes the dominant mechanism of deposition for particles less than 0.5 micrometers. Hence, the highest probability of particle deposition due to diffusion occurs for very small particles inhaled into acinar region of the lungs.

3.5. Factors affecting the delivery of aerosolized drugs

In aerosol therapy, the drug appears as solid particles in liquid, which is then aerosolized. The size of these drug particles in aerosol is referred to as a droplet size. The fraction of the aerosolized drug eventually delivered at the target site depends on defense mechanisms of the respiratory tract. The effectiveness of defense mechanisms can dependent on properties of the aerosol or the hot factors of the target. Khilnani and Banga (2008) identifies that the physical properties of the aerosol affecting to the delivery of aerosolized drugs to the lungs are:

- droplet size (mass median aerodynamic diameter),
- density,
- electrical charge,
- hygroscopy,
- shape, and
- velocity of the aerosol particles.

When the host factors affecting to the delivery of aerosolized drugs to the lungs are:

- inspired volume,
- inspiratory time,
- inspiratory flow,
- breath-hold duration,
- timing of aerosol delivery during inspiration, and
- airway status and the lung pathology.

3.5.1. Effect of physical characteristics of aerosol to the drug delivery

The deposition of the aerosol is impacted by physical characteristics of it, which is dependent on the drug, the formulation of medication and the aerosol generator. As stated by Khilnani & Banga (2008) the droplet size is the most important factor in the delivery of the drug to the lungs. The aerosol with droplet size larger than five

micrometers tends to be filtered out in the upper airways, when aerosol with droplet size less than five micrometers (Khilnani & Banga, 2008) usually reaches the distal areas of the respiratory tract. Particles with size from two micrometers tend to deposit in the conducting airways, when particles down from two micrometers (Hasan, 2010) deposit in the alveoli. This hold true down to the size of 0.5 micrometers, as according to Ruickbie et al. (2011) smaller particles than that tend to be exhaled. For this reason, Cole (2000) recommends that the optimal aerosol particle size for adults is in range of 0.5 to five micrometers.

Chemical and physical properties of the drug may also affect the delivery of the aerosol, but they mostly determine the penetration of the drug in deposition site. Also, the velocity of the drug affects the site of deposition, because particles with velocity can deviate from their initial path and to impact on airway walls. For this reason, aerosols that are generated at very high velocity tend to get deposited in the upper airways. In addition, if the drug has hygroscopic properties it is likely to increase size in humid condition, and the delivery of the drug is reduced. (Khilnani & Banga, 2008)

3.5.2. **Effect of host factors to the drug delivery**

Host factors can be divided to those considering the airway status of the patient and those considering the ventilation of the patient. The factors considering ventilation are inspired volume, inspiratory time and timing of delivery during inspiration. With higher inspiration volume and timing of inspiration a higher amount of the drug is delivered to the lungs and thus the quantity of particles deposited is increased. Darquenne et al. (2000) have indirectly proved that the holding of breath will increase deposition with gravitational sedimentation mechanism. Based on these findings, it seems that the small respiratory rate increases the aerosol deposition.

Among the host factors, according to Khilnani & Banga (2008) the status of airways and the lung pathology do not affect the total amount of the drug delivered to airways, but they affect the site of deposition. This site is mostly dependent on the droplet size of the aerosol, but also the age of patient affects the target site. This is because the changes during the development of the lungs.

For the developed lungs of adults and pediatrics a droplet size distribution from one to five micrometers (Cole, 2000) provides highest deposition. In contrast, for the developing lungs of infant population droplet size approximately from two to three micrometers (Schulz, 1998) is preferred. In addition, Minocchieri et al. (2006) has showed that for preterm infant droplet size of 1.6 micrometers were optimal to minimize the impaction in the upper airways. For neonates the particles with size of one to two micrometers (Cole, 2000) may provide the greatest lung dose, because the small size of airways.

The pulmonary functions of the infants and neonates differ from the developed lungs of adults and pediatrics. For this reason, the dose delivered to the target site is also decreased by the lower tidal volume, lower inspiratory flow and increased respiratory rate.

3.6. Devices used for aerosol therapy

There are currently three classes of medical devices suitable for aerosol delivery: nebulizers, metered-dose inhalers and dry powder inhalers. Nebulizers can be divided in three types by the mechanism of breaking up the liquid into aerosol. These types are pneumatic, ultrasonic and vibrating mesh nebulizers.

3.6.1. Dry-Powder Inhaler

A Dry-Powder Inhaler, DPI, is an aerosol delivery device that delivers medication to the lungs in the form of a dry powder. A fixed volume of powder is placed at the end of a tube and drawn through the tube with inspiration. As the inspiration drawn gas through the tube, the powder aerosolizes either passively or due to an active dispersion mechanism. The air velocity required to generate the aerosol, usually varies among various DPIs models, but according to Borgstrom et al. (1994) a flow rate of 60-90 l/min is generally required. This makes DPI unsuitable for elderly, pediatric and neonatal patients, and patients with respiratory obstructions. (Hasan, 2010)

Everard et al. (1996) recognizes challenges in a use of DPIs with mechanical ventilation. Firstly, the operating principle of DPIs makes it hard to be used with ventilated patients. Using DPI with mechanical ventilation would require the opening of the breathing circuit and a constant coordination from the clinician during therapy. The aerosol should be first produced from powder and then introduced to the inspiratory flow from the ventilator. Secondly, warm and humidified gas in the breathing circuit affects the solid particles in aerosol. The effect of humid environments to solid particles in aerosol and the feasibility of administrating these in humid conditions are not well known.

3.6.2. Metered-Dose Inhaler

Metered dose inhaler, MDI, is an aerosol delivery device, which design are initially from year 1955 (Freedman, 1956) and has not changed much since. The MDI consist of a valve containing the drug, an actuator booth to trigger the aerosolization of the drug and a tube to direct the aerosol towards the mouth. The drug in the valve is stored under pressure in micronized form and is released from the canister through a metering valve and stem. The stem fits into an actuator boot, which aerosolize the drug. The actuator boot is always designed and tested to work with specific drug formulations, which has a

twofold effect. Firstly, MDIs have an ability to produce uniform particle size, which increases the efficiency of reliable drug delivery. In other hand, the requirement for specific drugs limits the number of drugs available for MDIs. (O'Callaghan & Wright, 2002)

According to Ruickbie et al. (2011) the use of MDIs with mechanically ventilated patients is employed only in a minority of hospitals. Dhand (2004) presents two reasons for that. Firstly, the amount of drugs available for MDI is limited, if you compare it to drugs for nebulizers. Secondly, the use of nebulizers is simpler for aerosol therapy with mechanical ventilation.

3.6.3. **Pneumatic Nebulizer**

Pneumatic nebulizers are also referred to as jet nebulizers. The operating principle of these nebulizers for aerosol production is presented in Figure 3-3. This operation principle bases on the gas flow passing through the nebulizer in order atomize the drug in a reservoir of the nebulizer. (Vecellio, 2006)

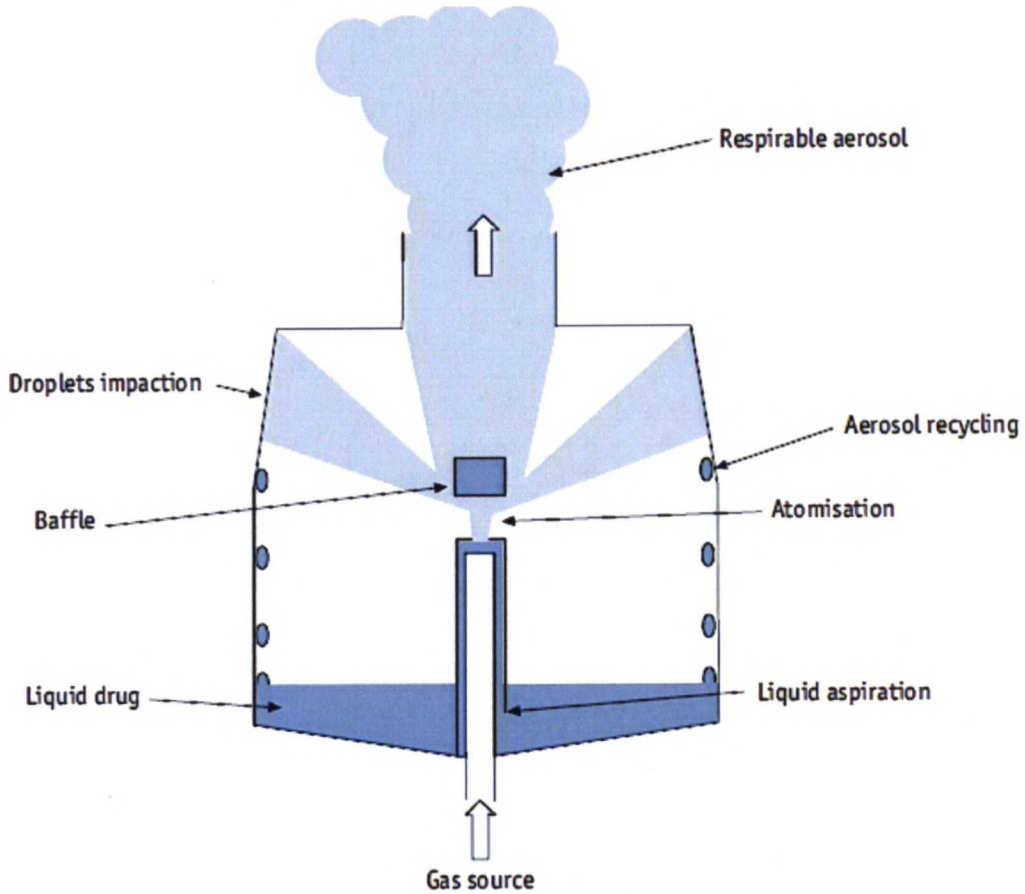

Figure 3-3. The pneumatic nebulizer. (Vecellio, 2006)

In a pneumatic nebulizer the liquid drug solution is at the bottom of the reservoir. To aerosolize the drug solution a gas flow is passed through a tube located in the middle of the bottom of the reservoir. The narrow diameter of this tube this causes the velocity of the gas to increase. This increase in velocity also draws the drug solution into fine ligaments, which then shatter into droplets with the forces of surface tension. These droplets are driven to a baffle, which directs large droplets to the side of the reservoir to be recycled. According to Vecellio (2006) more than ninety percent of droplets are recycled. Finally, droplets with smaller size are transported out of the nebulizer by the gas flow. (Nerbrink, et al., 1994)

Because of the operating principle of the pneumatic nebulizer, the drug mass loaded in the nebulizer is greater than that delivered. The part of the drug that eventually will not be delivered out of the nebulizer is refereed as residual mass. Vecellio (2006) also points out that because of the operating principle, they cannot aerosolize all types of drug mixtures. Firstly, the operating principle can partially destroy the brittle drug compounds due to the mechanical stress of aerosolization. Secondly, since according to Hasan (2010) during aerosolization more water than drugs leaves nebulizer, the drug concentration of the solution within the reservoir increases. This difference in output characteristics may have relevance with drugs that require tightly controlled dosage.

The pneumatic nebulizer is undependable on patient breath coordination, which makes is suitable to be used during ventilation and by patients with limited tidal inspiration. The continuous delivery also requires less patient or clinician coordination.

3.6.4. Ultrasonic Nebulizer

Ultrasonic nebulizers, presented in Figure 3-4, use the vibration of a piezo-electric crystal at the bottom of the nebulizer to generate the aerosol from liquid solution. This crystal with 1.2-24 MHz (Hasan, 2010) vibration generates standing waves, which crest of these standing waves fracture into droplets. Similar to pneumatic nebulizers the large droplets are thrown to the side of the container and recycled, when small droplets leave the nebulizer. In comparison to pneumatic nebulizers, ultrasonic nebulizers do not require external source of gas flow, because they can operate with the inhalation of the patient or the inspiration flow of the ventilator.

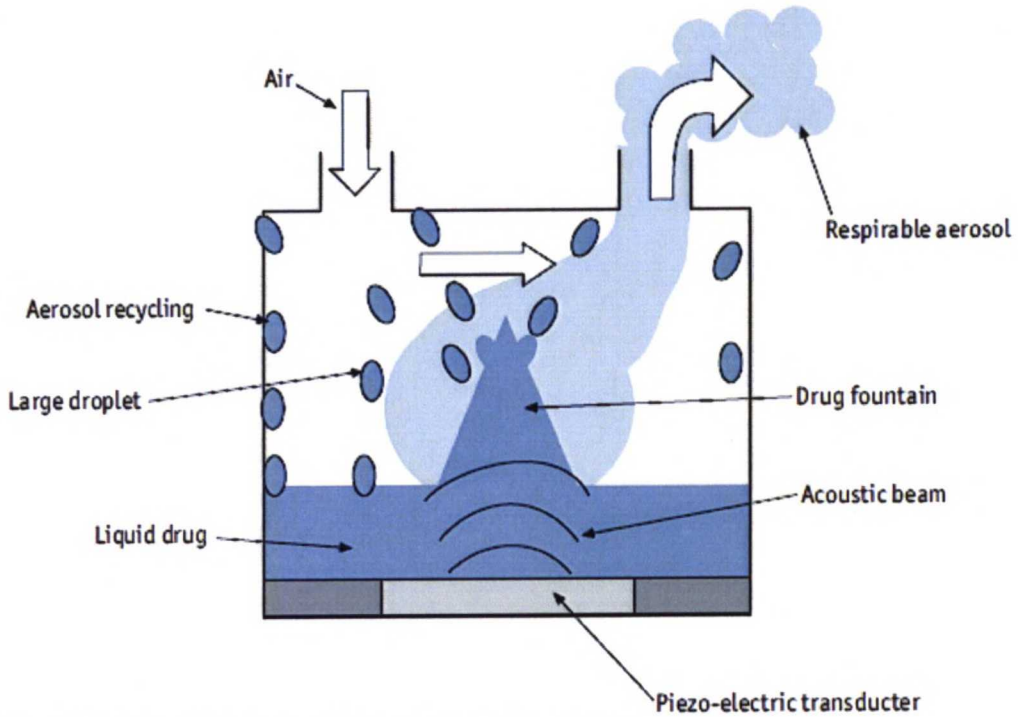

Figure 3-4. The ultrasonic nebulizer (Vecellio, 2006)

According to Hasan (2010) the droplet size of the aerosol is inversely proportional to the vibration frequency. Therefore, it is the frequency that determines not only the droplet size, but also affects the output rate of the ultrasonic nebulizer. As a result of the operating principle, some of the drug is trapped inside the ultrasonic nebulizer. This residual mass increases the drug wastage with ultrasonic nebulizers.

There are two main challenges with ultrasonic nebulizers. Firstly, as Dhand (2008) states the nebulizer heats during operation, this causes the temperature of the drug to increase by ten to fifteen degrees. Nikander et al. (1999) have proved that because of this warming, ultrasonic nebulizers do not effectively aerosolize suspensions or liquids with high viscosity or high surface tension. Secondly, ultrasonic nebulizers require external source of power to generate the vibration of a piezo-electric crystal. Regardless, with portable power source the nebulizer unit of an ultrasonic nebulizer can be portable and convenient to use. In addition, Dhand (2008) suggests that as result of more technical design, ultrasonic nebulizers are much more expensive than pneumatic nebulizers.

Despite the few limiting factors, ultrasonic nebulizers have advantages compared to pneumatic nebulizers. O'Doherty et al. (1992) have studied that ultrasonic nebulizers have higher rate of nebulization and require shorter time of operation than pneumatic nebulizers. Ultrasonic nebulizers are also able to operate intermittently or continuously. Also, Harvey et al. (1997) have studied that ultrasonic nebulizers are generally more efficient with mechanical ventilation than pneumatic nebulizers.

3.6.5. **Static Mesh Nebulizer**

Mesh nebulizers are the latest technology introduced for nebulization. The characteristic feature of mesh nebulizers is a mesh plate with thousands holes. The diameter of these holes determines the size of droplets generated, because the drug is pushed through the mesh plate. The first type of mesh nebulizers was a static mesh nebulizer, which is presented in Figure 3-5 presents a static mesh nebulizer, which was the first type of mesh nebulizers. The static mesh nebulizer uses vibration of piezo-electric crystal to push the drug through the mesh plate. (Vecellio, 2006)

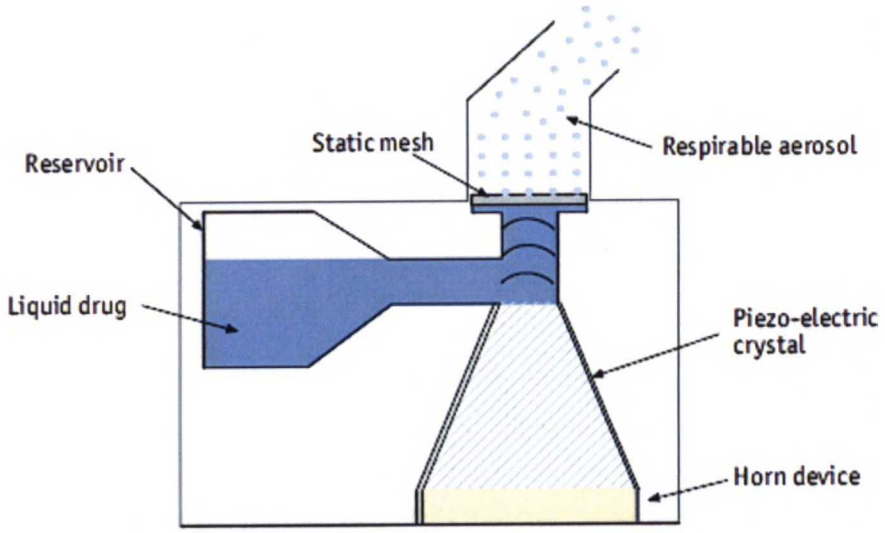

Figure 3-5. The static mesh nebulizer (Vecellio, 2006)

Comparison to pneumatic or ultrasonic nebulizers the aerosol is not recycled in static mesh nebulizer, but eventually the residual volume in the reservoir of the nebulizer is lower than in pneumatic or ultrasonic nebulizers. The technique used in static mesh nebulizers was further developed to vibrating mesh technology. Due to this static mesh nebulizers are not very common, and most of recently introduced mesh nebulizers are based on the vibrating mesh technology instead of the static mesh technology.

3.6.6. **Vibrating Mesh Nebulizer**

The latest development of mesh nebulizers is vibrating mesh nebulizer, which design is presented in Figure 3-6. Compared to static mesh nebulizer the piezo-electric actuator is in contact with the mesh plate and the operation is based on the vibration of this mesh plate. Also, the drug reservoir is located above the mesh and aerosol is produced downwards. The holes in the mesh have a conical structure with the largest cross section of the cone in contact with the drug. (Vecellio, 2006; Knoch & Keller, 2005)

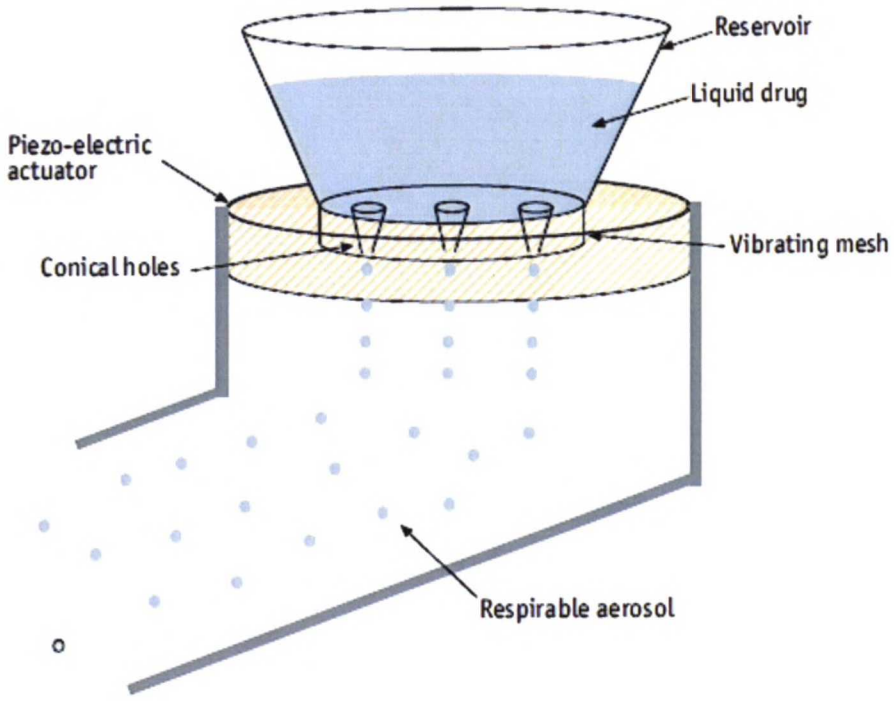

Figure 3-6. The vibrating mesh nebulizer (Vecellio, 2006)

As a result of vibration, the mesh is constantly moving up and down. This movement loads holes with drug solution and simultaneously ejects droplets to the other side. Because the drug solution is located above the mesh plate, droplets are ejected downwards producing a cloud of aerosol. Due to the design of the vibrating mesh nebulizer the residual volume is negligible and dependable on position of the nebulizer. (Vecellio, 2006)

The droplet size produced by vibrating mesh nebulizer is mainly determined by the diameter of the holes in the mesh plate. Currently commercialized mesh nebulizer, presented in Table 3-2, produces particle with a mass median aerosol diameter from three to seven micrometers. Stangl et al. (2003) presents that in addition to the hole size of the mesh plate, also the physical properties of the drug formulation slightly influence the droplet size. However, Simon et al. (2001) have studied that main factor the drug formulation influences is the output rate. As stated by Vecellio (2006) this output rate can also be decreased by suspensions with a high surface tension can decrease the output rate of vibrating mesh nebulizers. It is also possible that suspensions with a high surface tension cannot pass through the holes in mesh plate and only block these holes. This becomes a challenge when producing droplets with a smaller size, because the holes with a smaller diameter increase the occurring possibility of the blockage.

Table 3-2. Performance of different mesh nebulizers. (Vecellio, 2006)

Name	MMAD (μm)	Output rate (ml/min)	Residual volume (ml)
Micro air NE-U22V	4-7	0.2-0.3	0.3
Aeroneb Pro	3-5	0.3-0.5	<0.3
eFlow repid	3-5	0.3-0.7	>1.2
Pari LC+	4-6	0.2-0.3	>1.2

As ultrasonic nebulizers also vibrating mesh nebulizers can operate intermittently or continuously. Also they do not require external gas flow to operate. In contrast, the produced cloud of aerosol with a low velocity can be directly inspired by the patient or introduced to the inspiratory flow of the ventilator. In comparison to ultrasonic and pneumatic nebulizers, the droplet size produced with vibrating mesh nebulizer is determined by the design and not affected by the operating settings, because the size of holes in the mesh plate eventually determines the size of particles passing through the mesh plate. As a result of these features, vibrating mesh technology provides possibility for the more precise control of the droplet size than other nebulization technologies.

4. Aerosol therapy with mechanical ventilation

There can be several goals for beneficial aerosol therapy, and as presented by Dhand (2004) the main ones are:

- high efficiency of the drug delivery,
- reproducible dosing,
- targeted delivery to site of the action,
- ease of the operation of the device,
- short duration of the treatment,
- minimized risk to the patient and the clinician,
- environmental protection, and
- cost-effectiveness of the treatment.

These goals are also valid when the nebulization treatment is administrated with mechanical ventilation. In this chapter mechanical ventilation, efficiency of nebulization during mechanical ventilation, and the medications used in nebulization with mechanical ventilation are discussed. In addition, the solution of the case company for the nebulization with mechanical ventilation is presented at the end of this chapter.

4.1. Mechanical ventilation

Inflow and outflow of air between the atmosphere and the lungs is referred to as ventilation. If the respiratory system is unable to maintain adequate ventilation, mechanical ventilation is used for performing the breathing. Most common reasons for mechanical ventilation are the acute respiratory failure or relaxation of respiration muscles as a result of administration of anesthetic drugs.

Mechanical ventilation is performed by a mechanical ventilator, which is a medical device that provides an artificial ventilator support. Mechanical ventilators are routinely used in various health care settings, which according to Cawley (2011) are hospitals, long-term care facilities, ambulances, mobile intensive care units, and life flight or helicopter transports. Mechanical ventilator produces a controlled flow of gas into a patient's airway. The flow of the gas is based on a positive pressure generated by the ventilator to the upper airways. When the additional pressure is removed, the flow of the gas directs outwards.

Hasan (2010) classifies mechanical ventilation to invasive mechanical ventilation and non-invasive mechanical ventilation. In invasive mechanical ventilation the patient's upper airways are bypassed with an artificial airway, usually with endotracheal tube, ETT. The alternate method, non-invasive mechanical ventilation, does not require the bypassing of upper airways, because the breathing is supported noninvasively with a mask or nasal prongs.

In invasive mechanical ventilation the endotracheal tube is connected to a breathing circuit, which includes inspiratory and expiratory hoses connected to the mechanical ventilator. The connection of the endotracheal tube and inspiratory hoses are done by a y-piece. In addition, between the y-piece and the endotracheal tube there usually are also other connectors. These can be a flow sensor, a gas measurement adapter, adapter for positive end-expiratory pressure saver port, and a heat and moisture exchanger. These additional components increase the mechanical dead space and increases the effort required for ventilation (Datex-Ohmeda, 2007). This increase in dead space has even more importance with patients with lover tidal volumes. (Cheifetz, 2003)

There are many methods by which the patient and the ventilator interact to perform the ventilator cycle. These variable methods are called modes of ventilation and Cawley (2011) categorize these methods based on the degree of support and cycling of the flow.

Firstly, mechanical ventilators can either provide full artificial support or partial support for ventilation. With full artificial support gases are delivered regularly without detecting the breathing efforts by the patient. In comparison, when the ventilator detects spontaneous breathing efforts and supports them, the ventilator provides partial support.

Secondly, the flow of the ventilator is traditionally classified as volume, pressure, or time cycled. Volume cycling ends when a predetermined volume is delivered, pressure cycling ends when a preset pressure level is reached, and time-cycling ends when a timing mechanism in the ventilator reaches a preset duration. Full support mode using pressure-regulated method is called pressure controlled ventilation, PCV, and when using volume-regulated method it is called volume controlled ventilation, VCV. (Cawley, 2011)

Mechanical ventilator directs a positive pressure to the lungs for the inspiration and removes the additional pressure for the expiration. The positive pressure maintained within the lungs after the exhalation phase is referred to as positive end-expiratory pressure, PEEP. According to Cawley (2011) the primary role for PEEP is to increase the functional residual capacity. This increase in the functional residual capacity increases the surface area of the alveoli, allowing greater surface area for oxygen to transfer into the pulmonary circulation.

When the patient no longer needs ventilator support he is weaned from the ventilator. It is done by reducing the support the ventilator gives to the patient's spontaneous breathing. This weaning may take from few hours to several days (Datex-Ohmeda, 2007), depending on the patient's condition. When it has been established that the patient is able to breath easily on his own, the endotracheal tube is removed. This removing of the endotracheal tube is referred to extubation.

4.2. Factors effecting the efficiency of the nebulization treatment

Dhand (2008) suggests that a successful delivery of aerosol to the lungs of the patient depends on the ability to optimize several factors. These factors can be classified into four categories: factors related to the device, factors related to the breathing circuit or the ventilator, factors related to the patient, and factors related to the drug. These factors influence to the deposition site and quantity of the drug, but Gonda (2004) notifies that these influences also to the proportion of the drug deposited in the breathing circuit and the artificial airway.

The efficiency of the nebulization treatment is eventually determined by the quantity of the drug deposited in the target site. The efficiency of nebulization treatment consists from the precision, the reliability and the consistency of dosing. Precision of the deposition describes the amount of drug delivered to the target site, while reliability describes the uniform of drug deposition in the lung under variety of conditions. Consistency of dosing requires uniformity in drug deposition between two different aerosol treatments. (Dhand, 2008)

4.2.1. Factors related to the device

There are several factors related to the device that affects the efficiency of the nebulization treatment, and these factors are

- the type of the nebulizer,
- the position of the nebulizer in the breathing circuit,
- duration of the nebulization,
- the intermittent or continuous cycling,
- the synchronization of the nebulization with the ventilator,
- the additional gas flow,
- the fill volume of the nebulizer, and
- the residual dead volume of the nebulizer. (Dhand, 2008)

There are three different types of nebulizers: Pneumatic Nebulizers, Ultrasonic nebulizers and Vibrating mesh Nebulizers. The type of the nebulizer also affects other factors, because each nebulizer type has specific requirements related to these factors. The operating principles of different types of nebulizers are discussed in Chapter 3.6 and Table 4-1 presents the characteristics of these nebulizers.

Table 4-1. Characteristics of different aerosol generators used for ventilated patients (Mazela & Polin, 2011).

	Pneumatic Nebulizer	**Ultrasonic Nebulizer**	**Vibrating mesh Nebulizer**
Principle of aerosol generation	Pressurized gas forms a jet passing over a capillary tube that draws liquid formulation into the jet stream	Piezoelectric crystal converts an electrical signal into high-frequency vibrations and creates a standing wave in the medication and produces aerosol	Aerosol is produced by micro pumping action of the vibrating mesh containing 1,000 funnel-shaped holes
Gas flow	Active	Passive	Passive
Recommended location within circuit	Inspiratory arm	Inspiratory arm	Inspiratory arm or between Y-piece and ET tube
Residual volume	Large	Small	Small
Aerosol particle size	Depends on gas flow and formulation	Depends on formulation	Depends on mesh and formulation
Aerosol temperature	Low	Ambient	Ambient
Efficacy expressed as inhaled dose of nominal dose	Lower	Mid	Higher

The type of the nebulizer affects the droplet size of generated aerosol. This has major effect on the efficiency, because as stated by Khilnani & Banga (2008) the droplet size is the most important factor effecting to the delivery of the drug to the lungs. The reason for this is that the droplet size affects both the deposition site and the deposition quantity.

For this reason, the type of the nebulizer has a major effect on the efficiency of the efficiency of the nebulization with invasive mechanical ventilation. Studies have proved vibrating mesh nebulizers at least 60 % (Vecellio, et al., 2008) more efficient or that inhaled percent of dose delivered by the vibrating mesh nebulizer was between two to four fold (Ari, et al., 2010) greater.

The location of the nebulizer in the breathing circuit will affect the drug delivery. O'Doherty et al. (1992) have proved that with continuous nebulization the placement of the nebulizer unit farther away from the patient improves the quantity of aerosol eventually depositing to the lungs. The reason for this is that the inspiratory hose of the

breathing circuit acts as a spacer for the aerosol to accumulate between breaths. Though, this study did not evaluate total efficiency, as it neglected the amount of aerosol deposited in the breathing circuit. Ari (2010) compared efficiency of the pneumatic nebulizer, ultrasonic nebulizers and vibrating mesh nebulizer placed in three different positions in normal and in humidified conditions. The positions were: between the breathing circuit and endotracheal tube, six inches away from the y-piece in the inspiratory limb of the breathing circuit, six inches away from the ventilator in the inspiratory limb of the breathing circuit. Six inches away from the y-piece in the inspiratory limb of the breathing circuit proved to be the most effective placement for the ultrasonic and the vibrating mesh nebulizer. The pneumatic nebulizer was most efficient when placed six inches away from the ventilator.

Ari et al. (2010) proved the inefficiency of position where both the expiration and the inspiration air flow. This may be due to pressurization and expansion of the expiratory limb of the ventilator circuit that occurs before the gas from the ventilator is directed down the endotracheal tube. In other hands, the position near the patient airways would reduce the volume of the space between the nebulizer and the patient. This position has the capability to increase the efficiency, since as stated by Ari & Fink (2010) the tidal volume used in the ventilation should be larger than the volume between the patient airways and the nebulizer. Especially with small patients with lower tidal volumes, the volume inside the breathing circuit can exceed the tidal volume of the patient.

Nebulizers may operate continuously or intermittently with an internal timing or external signal. Miller et al. (2003) have studied that intermittent nebulization is more efficient for aerosol delivery than continuous nebulization, because it minimizes aerosol loss during exhalation. According to the studies of Miller et al. (2003) when nebulization is synchronized with inspiration flow, its efficiency is enhanced as much as four times more than with continuous nebulization. This is because if aerosol device is positioned between the breathing circuit and the endotracheal tube, the continuous nebulization would cause the drug to enter the expiration limb during the expiration phase. For this reason intermittently nebulization can be seen as requirement, when nebulization device is positioned between the breathing circuit and the endotracheal tube.

In comparison to studies of Ari et al. (2010), a study conducted by Turpeinen & Nikander (2001) showed that ventilator synchronized nebulization and placement of the nebulizer directly below the y-piece resulting the highest deposition in infant test lungs. They compared synchronized and non-synchronized nebulizer positioned either in the inspiratory limb or between the breathing circuit and the patient's airways. This may suggest that the effect of location and synchronization to efficiency are cross-linked.

Residual volume is the amount of medication remaining in the nebulizer at the end of a treatment, and generally it ranges from 0.1 to 2.4 milliliters (Ari & Fink, 2010). The greater the residual volume, the less amount of drug is nebulized. According to Dhand (2008) if the fill volume is near the residual volume, nebulizers do not function well.

For this reason, ultrasonic nebulizers and vibrating mesh nebulizers with a smaller residual volume are more suitable for smaller doses.

4.2.2. Factors related to the breathing circuit or the ventilator

Because the nebulizer is positioned in the breathing circuit, both the ventilator and the breathing circuit effects the efficiency of the nebulization therapy for mechanically ventilated patient. According to Dhand (2008) the factors related to the ventilator that affect the efficiency are

- ventilation mode,
- tidal volume,
- respiratory rate,
- duty cycle,
- inspiratory waveform, and
- breath-triggering mechanism.

The factors related to the breathing circuit are

- the size of the endotracheal tube,
- humidity of inhaled gas, and
- density of inhaled gas.

Ari & Fink (2010) have investigated that the mode of ventilation is one of the main ventilator related factors that influences the aerosol delivery. Hess et al. (2003) have proved that aerosol delivery with a pneumatic nebulizer in pressure controlled ventilation has been twofold greater compared to delivery in volume controlled ventilation. In addition to this, Mazela & Polin (2011) have proved that maintaining the positive end-expiratory pressure during the ventilation increases the delivery. Besides the ventilation mode, also the tidal volume of the ventilation affects the efficiency, and it should be larger than the volume between nebulizer and the patient. This is because the aerosol is delivered to the lungs during the inspiratory.

The majority of ventilator related factors effects during continuous nebulization, and are less significant with synchronized nebulization. Duty cycle is the ratio of inspiratory time to total breathing cycle, and the increase in duty cycle obliviously increases the rate of aerosol delivery. Are & Fink (2010) have investigated that with continuous nebulization the increase in duty cycle directly increases the efficiency, but similar effect with synchronized nebulization has not been proved. In order to reduce the patient's work of breathing, many modern ventilators utilize continuous trigger or bias flow through the ventilator circuit. Ari & Fink (2010) have investigated that with continuous nebulization both of these reduces the aerosol delivery.

According to Ari & Fink (2010) it has been shown that with synchronized nebulization the efficiency is mostly affected by the inspiratory flow. Lower inspiratory flows

improve aerosol delivery with mechanically ventilated patients, because the higher inspiratory flow rate increases turbulence and the inertial impaction of aerosol particles.

Ari & Fink (2010) also suggest that the decrease in inner diameter of endotracheal tube reduces the efficiency aerosol delivery. On intubated patient the endotracheal tube is narrower than the trachea, and for this reason the small inner diameter increases the deposition to the tube. In controversy, Dhand (2000) notifies that because endotracheal tube is narrower than the trachea, it provides more laminar flow path than the airways and increases the efficiency. As a result, the endotracheal tube increases the efficiency of the aerosol delivery compared to if the upper airways are not bypassed.

Active heated humidifiers may reduce aerosol drug delivery up to forty percent (O'Riordan, et al., 1992) compared to not heated and humidified breathing circuits. Although this effect caused by the increase of humidity is documented in literature, the causes, and thus possible solutions are less clear.

4.2.3. **Factors related to the patient**

The host effect of the aerosol deposition is already discussed in Chapter 3.5. The factors affecting the efficiency of the nebulization with mechanical ventilation considers either the status of patient's airways or the ventilation of the patient, and these factors are:

- severity of the airway obstruction
- mechanism of the airway obstruction
- presence of dynamic hyperinflation
- patient-ventilator synchrony. (Dhand, 2008)

Lipworth & Clarke (1997) have studied that airway obstruction reduces the efficiency, because they decrease the airway caliber. It is ironic, that the air flow obstruction that produces the need for aerosol therapy also decreases the efficiency of that therapy. In addition, with ventilated patients, the synchrony of ventilation between patient and the ventilator affects to the breathing pattern of the patient.

4.2.4. **Factors related to the drug**

In aerosol therapy, the drug is particles in liquid. The formulation of drugs varies between different medications and even drugs that eventually cause the variation in the droplet size. The effect of physical characteristic of the drug is discussed in Chapter 3.5, and the major drug related factors affecting with mechanical ventilation are:

- dose
- formulation
- droplet size
- targeted site for delivery.

The droplet size has major effect on the efficiency of the aerosol therapy, and it may be dependent of the formulation of the drug. Firstly, the formulation defines the type of nebulizers and thus the possible droplet size. Secondly, the droplet size may also be directly dependent of the drug formulation, since the drug itself may set lower limit for the droplet size.

Hasan (2010) has investigated that particles with a droplet size smaller than 0.5 micrometers tends to be exhaled out with expiration flow, and particles larger than five micrometers are deposited in the breathing circuit never reaching the lungs. Probable deposition sites of particles between these limits related to the droplet size are presented in Figure 4-1. Particles with size between 0.5-2 micrometers deposit in alveoli, when particles up from two micrometers tend to deposit in the conducting airways.

< 0.5 µm	0.5 – 2 µm	2 – 5 µm	> 5 µm
Exhaled out	Deposition in alveoli	Deposition in the conducting airways	Deposition in the breathing circuit

Figure 4-1 The site of deposition with mechanical ventilation related to the droplet size.

4.3. Medications used for aerosol therapy

Ruickbie et al. (2011) defines medication as any substance that is used in treating disease. In literature, and in common language, there is no clear distinction between the terms medication and drug. In this study medication is used as overall classification of specific drug types that are designed to alter the body function. Administration is the delivery of a medication to a patient, and it can be performed in various dosage forms such as tablets, capsules, or aerosol. There are also many variations in the routes of administration, including intravenous and inhalation. According to Rubin (2010) not all medications administrated intravenously are available to be used through inhalation, because the route of administration is dependent on the form that is dependent on type of the drug. The aerosolized form used in aerosols is achieved with different formulation.

The drug is usually administrated with formulation. Rubin (2010) defines a formulation as a structure that ensures that the right concentration of the drug is delivered to the correct part of the body. Formulations for nebulization are generally suspensions having drug substances and one or more consolvents, which are substances that dissolve while added to another substance.

According to Amani et al. (2011) use of conventional formulations lead to larger droplet sizes, because relatively large particle sizes of them. This is likely to lead to an unwanted drug deposition in the lungs. Also, many physical and chemical factors influence to the action of aerosol, e.g., viscosity and tonicity. Generally, formulations for aerosols should be isotonic, which means having equal tension.

The possible increase in clinical outcome with more developed drugs provides rationale to develop alternative formulations for aerosols. In addition, new formulations may allow controlled drug release that reduces the frequency of drug administration and systemic adverse effects. A detailed discussion of the various drug formulations under development are beyond the scope of this study, but Ruickbie et al. (2011) indicates that examples of new formulations under development are liposomes, nanoparticles and nanosuspensions.

According to Ruickbie et al (2011) the most commonly prescribed medications for nebulization with mechanical ventilation are bronchodilators. In addition to bronchodilators, also corticosteroids, antibiotics, mucolytic agents and vasodilators are administrated through the inhalation route for ventilated patients. The latest development of nebulization technologies has also increased the development of medications for nebulization.

4.3.1. **Bronchodilators**

Bronchodilators are medications that dilate the bronchi and bronchioles, making airways larger and decreasing the resistance in the respiratory track. This allows air to pass through the lungs easier. In addition to this action, Mutlu & Factor (2008) proved that some bronchodilators enhance alveolar fluid clearance in experimental settings.

Bronchodilators available can be categorized according to the way in which they widen or dilate airways (β2-agonist, anticholinergic or theophylline) or how long they work (short- or long-acting bronchodilator). Short-acting medications affect with a short reaction time and provide a quick relief from acute bronchoconstriction. Long-acting bronchodilators are used to help to control and prevent symptoms.

Formulations suitable for aerosols exist in category of short-acting anticholinergic and in category of short- and long-acting β2-agonist. When theophylline is only available in tablet or liquid form and is not suitable for nebulization. The bronchodilators suitable for nebulization are:

Short-acting β2-agonists

- albuterol / salbutamol,
- fenoterol,
- isoetherine,
- isoproterenol,
- levalbuterol,

- metaprotenol,
- terbutaline, and
- tornalate.

Long-acting β2-agonists

- formoterol, and
- salmeterol.

Short-acting anticholinergic

- ipratropium, and
- bromide. (ATS, 2012)

β2-agonists are medications that mainly effect the muscles around bronchioles in airways. Muscle tightness around airways makes them narrower, which often results in breathlessness. β2-agonists work by relaxing muscles of airways, resulting in the widening of airways. Short-acting β2-agonists act within three to five minutes, but may only last from four to six hours. These medications are often given as reliever medications because they bring a quick relief for breathlessness. In comparison, long-acting β2-agonists last about twelve hours and are used to provide stable airways on a day-to-day basis. For this reason, long-acting β2-agonists are considered as maintenance drugs. Even though, β2-agonists mainly affect muscles in airways, they may also affect muscles in the heart and around the bones causing a fast heart beat and palpitations, which is a fluttering feeling in the chest. (ATS, 2012)

Another category of bronchodilators are anticholinergic drugs. While the β2-agonists affect muscles around bronchioles, anticholinergic drugs mainly affect muscles around the bronchi in large airways. Quite similar to β2-agonist, anticholinergic works by stopping muscles from tightening. Short-acting anticholinergic medications work in about fifteen minutes and last for six to eight hours. Anticholinergic medication does not have as many side-effects as β2-agonists. (ATS, 2012)

Generally regional targeting of bronchodilators to the proximal airways is more important than distal alveolar deposition for bronchodilators. To achieve this Usmani et al. (2005) suggest to enhance the efficiency by altering intrapulmonary deposition through the droplet size. Usmani et al. (2003) have also proved that deposition results can be achieved with particle sizes from 1.5 to 6 micrometers, with the larger particles producing the greatest clinical response.

While all bronchodilators widen airways, they work in different ways to do so. Therefore it is possible to combine bronchodilators in order to increase benefits. Currently, according to Ari & Fink (2010) bronchodilators are commonly administrated to all adult patients with mechanical ventilation. Although bronchodilators have an established role in aerosol treatment with mechanically ventilated patients, Jones et al. (2010) reminds that there is a distinct lack of evidence for or against bronchodilators for ventilated patients without severe obstructive lung disease.

4.3.2. **Anti-inflammatory drugs**

Anti-inflammatory drugs decrease swelling in the airways of the lungs. The majority group of aerosolized anti-inflammatory drugs are corticosteroids, but there are also non-steroid anti-inflammatories available to be administered another routes than inhalation. Categories of corticosteroids available aerosol form are:

- beclomethsone,
- budesonide,
- flunisolide,
- fluticasone, and
- triamcinolone. (ATS, 2012)

Aerosol therapy provides possibility for direct delivery to the target site with minimized systemic effect. For this reason, Gaude & Nadagoude (2010) suggest that nebulized corticosteroids might be an alternative to systemic corticosteroids. According to American Thoracic Society (ATS, 2012) negative side-effects from aerosol steroids are less likely than from other formulations. In addition, Ruickibie et al. (2011) notifies that corticosteroids have an effect on the physiological downregulation of β2 receptors. Thus, β2-agonist is recommended to be administrated with systemic corticosteroid therapy.

Generally, inflammation is present throughout the airways. Thus the relevant target site is not limited and it is important that inhaled corticosteroids would be able to reach all sites in the lungs. The recommended droplet sizes are only studied with metered-dose inhalers, and as result of these Leach et al. (2009) recommend droplet size in range of 1-4 micrometers, with increased lung deposition with a smaller droplet size.

4.3.3. **Antibiotics**

Antibiotics are medications that fight infections caused by bacteria, and they have been used for decades to treat chronic lung infections. There are several antibiotics and the selection between them depends on the type of infection. According to Luyt et al. (2009) antibiotics in formulations for aerosol therapy are:

Aminoglycosides
- tobramycin, and
- gentamicin.

Polymyxin
- colistin (polymyxin E), and
- polymyxin B.

Vancomycin.

The targeted delivery with aerosol therapy provides advantages for treatment with antibiotics, because as stated by AbuSalah & Dhand (2011) successful treatment of respiratory tract infections requires adequate concentrations at the site of infection. In addition, Studies by Hagerman et al. (2006) provides compelling data how targeted delivery reduces the infections in airways with aminoglycosides and colistins improves pulmonary function. Falagas et al. (2008) in turn presented how polymyxins where effective with pneumonia.

A droplet size ranging from one to five micrometers appears to be optimal for antibiotics therapy, because according to Kuhn (2001) the most beneficial target site for antibiotics are bronchioles, where the disease process usually begins and then extend toward the bronchi.

Although antibiotic nebulization appears attractive, it has some drawbacks. Firstly, antibiotics have a limited penetration into not healthy lung tissues, which results to variation in the dosage. In addition, another disadvantage is that according to Luyt et al. (2009) the aerosol antibiotics require costly formulations.

4.3.4. **Mucolytic drugs**

Mucus may narrow or block airways, making it difficult to breath. Mucolytic drugs reduce the viscosity of airway mucus by degrading their polymeric structure. This will improve the mucociliary clearance. Mostly the mechanism of action for mucolytic drugs is partly unknown or incompletely characterized. (ATS, 2012)

However, it should be noted that many mucoactive drugs have activities additional to their perceived activity on mucus. For this reason, it is challenging to categorize and list compounds that affect mucus, but according to Rogers (2007) the most commonly used mucolytic drugs classified based on mechanism of the action to improve mucociliary clearance are:

Mucolytics
- N-acetylcysteine,

Mucokinetics
- surfactants, and
- hypertonic saline.

Mucoregulators
- glucocorticosteroids,
- anticholinergics, and
- macrolide antibiotics.

Mucolytics improves the mucoliary clearance by reducing the viscosity of mucus. The most common drug with mucolytic mechanism is N-acetylcysteine, which has been used for many years in the treatment of patients with a variety of respiratory conditions. However, although N-acetylcysteine is considered a mucolytic drug, its mucolytic

activity is not yet well documented. N-acetylcysteine is known to dissociate bonds of mucus to reduce viscosity. In addition, it is also associated with a reduction of bacterial load in airways. According to Riise et al. (2000) this is probably because it reduces adhere abilities of bacteria.

Mucokinetic agents increase the kinesis of mucus, which effectively increase the transportability of mucus. Most common medications with mucokinetic mechanism are surfactants and hypertonic saline. Inhaled hypertonic saline is known to work by reducing the entanglements in mucus and hydrating mucus. Therefore, mucociliary clearance removes this mucus more easily. Elkins et al. (2006) have confirmed that the inhaled hypertonic saline improves mucus clearance and lung function, and is also well tolerated by patients in long-term administration. (Rogers, 2007)

Surfactants are complex mix of proteins and phospholipids forming a thin film in alveolar surface tension. According to Dhand (2004) this film lowers surface tension, which enables small alveoli to remain open. In Addition, surfactants reduce the effort needed to expand the lungs during inspiration, thus reducing the work of breathing. Also, surfactants aid clearance of mucus by decrease the adhesion of mucus. For these reasons, surfactant replacement therapy is used with many respiratory diseases. The major disadvantage of surfactant is the viscosity of them. For this reason they are difficult to aerosolize, as according to Dijk et al. (1997) they tend to foam and form stable bubbles during nebulization. As a result, lower-respiratory-tract delivery is inefficient and the majority of the aerosol is lost in the nebulizer and in the breathing circuit. (Rogers, 2007)

Mucoregulators are drugs that beside their initial action mechanism also reduce the producing of mucus in airways. There are drugs in categories of bronchodilators, antibiotics and anti-inflammatory drugs with this additional effect. (Rogers, 2007)

The optimal droplet size for mucolytic drugs depends on the target site, which can vary. Dolovich (2000) suggests that for moculytic drugs a droplet size from one to two micrometers provides the best delivery to the distal airways and alveoli, while a droplet size between two and five micormeters to the central airways.

4.3.5. **Vasodilators**

Pulmonary vasodilators are an important treatment for the pulmonary arterial hypertension, because according to Siobal (2007) they reduce pulmonary artery pressure, improve hemodynamic function and alter ventilation/perfusion matching. Vasodilators that target the pulmonary circulation are currently already administrated to neonatal, pediatric and adult patients in acute care settings. Though, majority of these drugs is administrated systemically with simultaneous undesired effect on blood pressure and oxygenation. Pulmonary vasodilation can be achieved with various therapies, and the mostly used medications in aerosol formulation are:

- Procyclins;
  - iloprost,
  - ipoprostenol,
  - treprostinil, and
  - prostanoids,
- phosphodiesterase inhibitors, and
- endothelin receptor antagonists. (Siobal, 2007)

Currently the vasodilators aerosolized with mechanical ventilation are procyclins, when phosphodiesterase inhibitors and endothelin receptor antagonists are under development in formulations suitable for nebulization. Iloprost was the first procyclin approved for treatment of pulmonary arterial hypertension via direct pulmonary delivery by route of inhalation. Later both Meyer et al. (1998) and Sood et al. (2004) have reported procyclins treatments that have had positive effects and even improved gas exchange in adults and infants patients. Though, according to Siobal (2004) the clinical outcome of prostacyclin therapy has not been proved in large, randomized, controlled studies. (Siobal, 2007)

In addition to aerosolized vasodilators, nitric oxide therapy is used for pulmonary vasodilation. Nitric oxide has been recognized as an important contributor to the maintenance of a normal vascular function and structure. It was the first selective pulmonary vasodilator approved, and it is also approved for the treatment of neonates with persistent pulmonary hypertension requiring mechanical ventilation. Though, inhaled nitric oxide therapies have several potential toxicities and toxic metabolites, and nitric oxide is unstable in the presence of oxygen. (Siobal, 2007)

The different mechanism of action pulmonary vasodilators makes combination therapy an attractive option. The combinations of vasodilators are not yet widely studied, but current experience suggests the use of doses less likely to produce adverse effects. Overall, the inhalation route with aerosol formulations offers advantage of avoiding some of the systemic effects of intravenous, subcutaneous, and oral administration. (Siobal, 2007)

4.4. The solution of the case company

The nebulizer of the case company bases on the vibrating mesh technology. This operating principle is discussed in Chapter 3.6.6. Technically the main difference of the case company's nebulizer to typical vibrating mesh nebulizers is the reservoir of the drug. In the case company's nebulizer, the reservoir of the drug is elastic without any void. In typical vibrating mesh nebulizers the force moving the drug through the mesh plate is gravitational force, which is achieved by positioning the drug chamber above the mesh plate. This same force is achieved in the nebulizer of the case company with the pressing force, when the elastic material of the reservoir contracts. This technical solution makes the operation of the nebulizer independent of the positioning.

The nebulizer of the case company would consist of three components, as presented in

Figure 4-2, The reservoir for the drug is inside an disposable drug chamber, which is the top component of nebulizer. Technically it would be possible to have either pre-filled drug chamber or drug chamber where the drug is filled with a syringe. The pre-filled drug chamber would require collaboration with pharmaceutical companies owning the drugs intended to be filled in the drug chamber. Another disposable component would be the atomizer with the mesh plate. The sensor body between atomizer and drug chamber would be reusable. In overall, the nebulizer of the case company would be small in size and light weighted. It would be clearly smaller and lighter than current ultrasonic nebulizers, and on par with advanced vibrating mesh nebulizers.

Figure 4-2. The case company nebulizer. Consisting of the drug chamber at the top, in the middle is the sensor body controlling the liquid flow to the atomizer located at the bottom of the nebulizer.

Another differentiator of the solution of the case company is the connection method and the placement of the nebulizer with the breathing circuit. In the solution of the case company the nebulizer device is planned to be placed in the y-piece of the breathing circuit as presented in Figure 4-3. The connection of the nebulizer to the breathing circuit is accomplished through a designed y-piece including a PEEP saver port. With this solution the number of adapters connected to the breathing circuit can be reduced, as one connector has twofold role. The y-piece is also designed to minimize the dead space in breathing circuit.

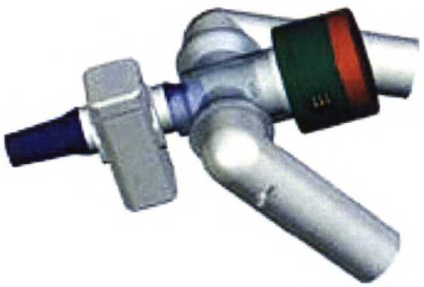

Figure 4-3. The nebulizer attached to y-piece connector of breathing circuit through PEEP saver port.

The setup with the nebulizer of the case company is presented in Figure 4-4, and it consists of the nebulizer unit, the designed y-piece, and a power line between the nebulizer and a control unit. The control unit can be in-built in the ventilator or external control unit.

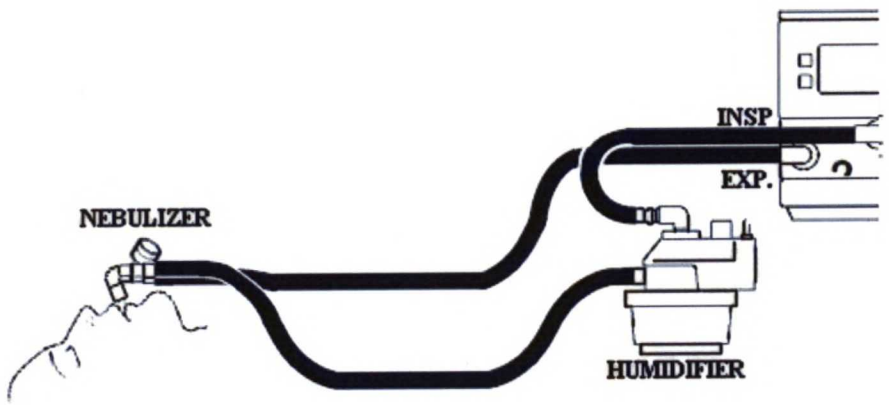

Figure 4-4. The setup for the nebulizer of the case company with mechanically ventilated patient.

There is also another possible setup available for the case company nebulizer. In this setup the nebulizer is connected through an adapter compatible for the case company nebulizer. The optimal placement for the adapter needs to be tested and proved. But based on the evidence with other setups with a vibrating mesh nebulizer, the optimal placement might be in the inspiratory hose of the breathing circuit.

PART III: THE MARKET STUDY

5. Research methods and tools

The objective of this research was the market situation analysis for the case company's solution. First this chapter describes the selection of research method to reach this objective. After that the chapter introduces data collection methods and tools used in this study. Finally, method for the analysis of this data is presented.

5.1. Research method

Colin & Hussey (Collis & Hussey, 2003) classifies a case study as a study that involves gathering detailed information about the unit of analysis with a view to obtain depth knowledge. According to Yin (Yin, 2003) case study is preferable choice as the research strategy when

- the study answers to questions how and why,
- the investigator has a little control over events under the study, and
- the focus of the study is on a contemporary phenomenon within some real-life context.

Furthermore, case study aims to provide description of a single instance of a phenomenon of interest within the given context of the study. The objective of this study is to evaluate the markets of nebulization solution for ventilated patients. To reach this goal, market situation analysis for the nebulizer of the case company is performed. As the settings of this study suits to these exceptions for a case study, it is selected as the research method for this study.

5.2. Data collection

The marketing research utilized by this study followed five steps of the marketing research process, presented in Figure 2-2. The research problem for interviews was generated from objectives of this study. The research plan was developed with assistance of the case company's Market Research Manager and Respiratory Global Product Manager, and the objectives for interviews were defined based on analyzes of pre-interviews and literature review.

Data gathered for this study with different data collection methods is presented in Figure 5-1. The interviews and discussion meetings were used as the primary data collection method in this study. Additionally, internal materials of the case company and external material were utilizes as secondary data sources. The purpose of secondary

data was to clarify the findings of interviews. Because of that, this study used both qualitative and quantitative data.

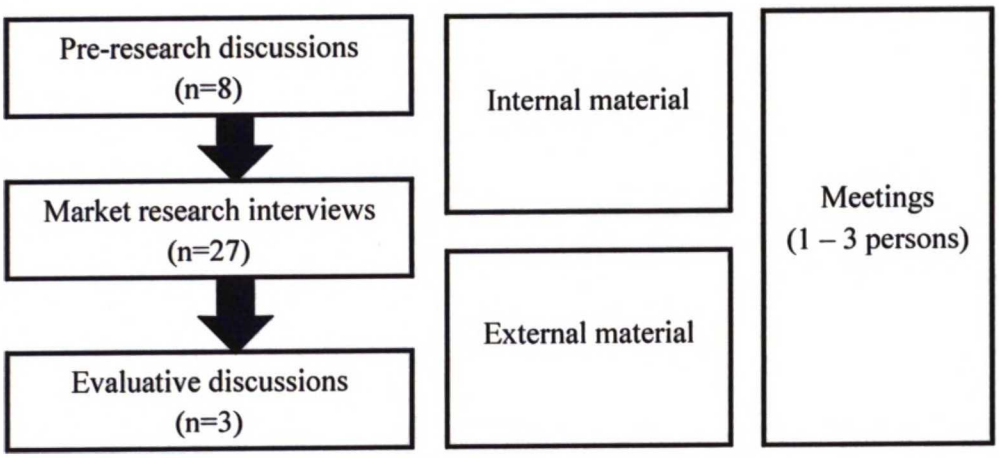

Figure 5-1. Data collection methods.

Interviews were used as one of the main data collection method in this study. During the study, a total of 38 interviews or discussions were conducted and list of these is presented in Appendix 1. Interviews were conducted in English or in Finnish, and made both face-to-face and through a telephone. Eighteen interviews were conducted in English and all the others were conducted in Finnish.

The pre-research discussions aimed at forming a view of history, development, and current state of aerosol therapy technologies, nebulization markets and other factors effecting nebulization therapy. Altogether eight people in the case company were selected for these discussions. The persons were chosen either because of their technology, marketing or clinical expertise in medical device business. The pre-research discussions were discussion-like meetings conducted in unstructured manner, which according to Hirsjärvi & Hurme (Hirsjärvi & Hurme, 2009) means that each question was formed based on the previous answer. The question areas were related to the expertise of the person and covered either the clinical, technical, or marketing aspect of the care areas where nebulization therapy is used. The information received from pre-research discussions adjusted the scope of study, revived the information gathered from literature and defined the structure of market research interviews.

The market research interviews were conducted for clinical experts in different care areas where nebulization therapy is used. Altogether three doctors and twenty four clinicians from high-acuity intensive care units or neonatal intensive care units were interviewed. The interviewees were selected based on suggestions of the Clinical

Research Manager of the case company. The interviews were conducted to broaden the understanding of current situation and challenges of in-hospital nebulization and to form an understanding of advantages and disadvantages of nebulizer features by clinical experts. Interviews were semi-structured, which according to Hirsjärvi & Hurme (Hirsjärvi & Hurme, 2009) means that they had some fixed questions and some aspects that were modified during the interview. This method allowed to follow the reactions and answers of the interviewees and to ask clarifying questions during the interviews. The interview structure is presented in Appendix 2.

Finally evaluative discussions were organized to ensure that the findings make sense and the key informants see the findings valid. The interviewees were selected from the pre-research interviewees and presented different expertise.

In addition to interviews, meetings with the case company personnel were one significant source of empirical data collection. There were two instructors form the case company, who usually attended to these meetings and significantly participated in discussions during the course of this study. In addition to case company instructors with technical and marketing expertise, there were meetings with personnel with clinical, pharmaceutical, marketing research or technology research specialization. During these meetings main findings of the study were discussed.

5.3. Analysis of the empirical data

From each interview notes were taken and analyzed using the methods of data analysis. According to Yin (Yin, 2003) the data analysis consists of examining, categorizing, tabulating, testing, or otherwise recombining both quantitative and qualitative evidence to address the initial propositions of a study. In general, data analysis means a search of pattern in data. For this, the relevant themes were identified and categorized for further analysis from the perspective of the interviewee's expertise. The data was finalized for presenting with several different methods including summaries from the issues emphasizes in the interviews.

Due to confidentiality issues, all the names of interviewees were removed. The data, however, was not modified.

6. Results

This chapter presents the marketing information gathered during interviews. At first, this chapter describes the nebulization treatment process utilized in hospitals. Secondly, different hospital setups for nebulization of ventilated patient are presented. Also, administration behavior of nebulization therapy, challenges related to nebulization therapy and drugs used with nebulization therapy are presented in this chapter.

6.1. Overview of the nebulization treatment process

The basic workflow of nebulization process for ventilated patient was generated based on the answers of the interviewees. The workflow consists of six steps: preparing the nebulization equipment, preparing the patient, preparing the ventilator circuit, delivering the medication, detaching the nebulization equipment and restoring settings of the ventilator, and handling nebulization equipment after the treatment. The workflow of nebulization treatment for ventilated patient is presented in Figure 6-1.

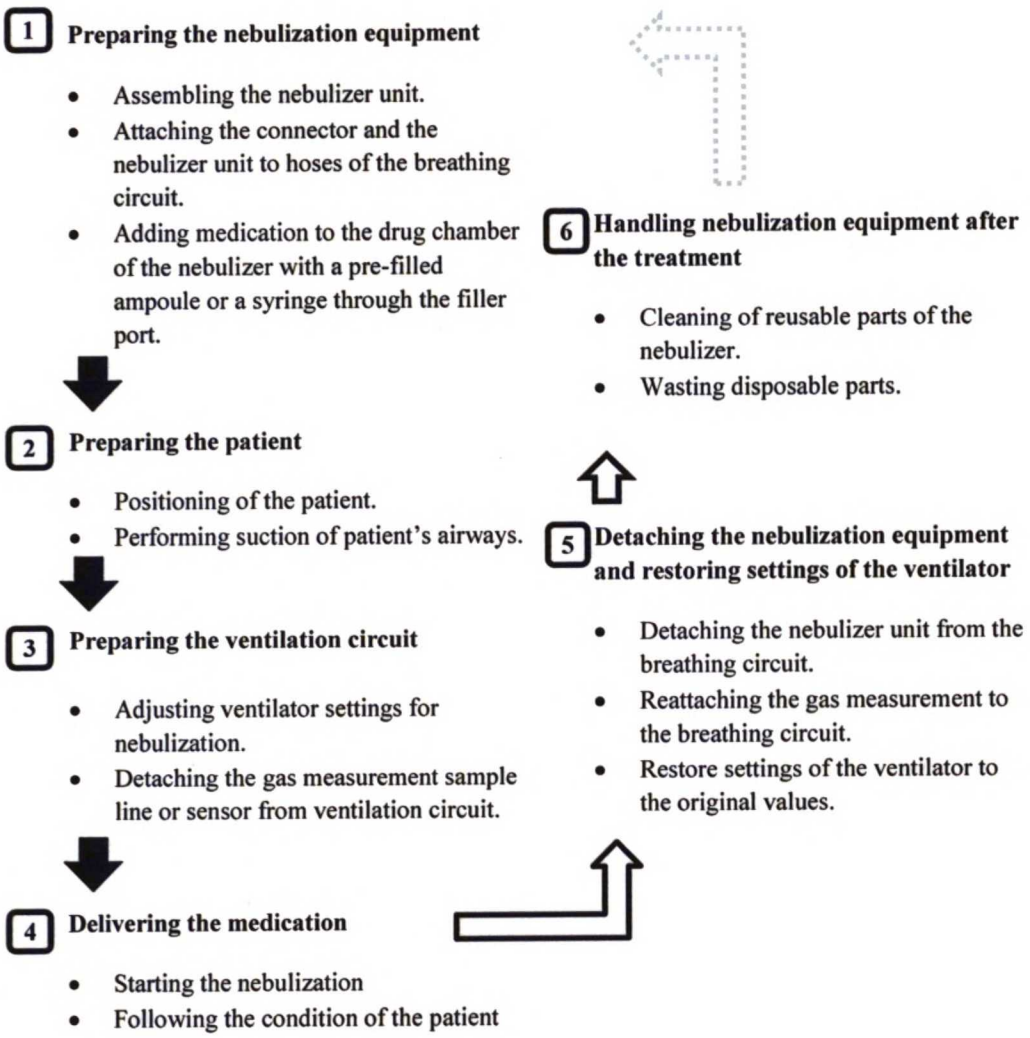

Figure 6-1. Overview of workflow of nebulization treatment for ventilated patient.

First step of the process is to prepare the nebulization equipment. Assembling method is dependable of the type of the nebulizer. Single-use nebulizers are ready for use after removing them from a sterile package. However, several nebulizers consist from single-use and re-use components. According to an interviewed nurse (Appendix 1, discussion 8) the assembly of single-use and re-use components is performed by the clinician. After the assembly of nebulizer units is completed it is connected to the breathing circuit. This is done with specific T-piece airway adapter. An interviewed nurse (Appendix 1, discussion 8) suggest that the most common connection point is in the inspiratory limb of the breathing circuit. The connection of additional airway adapter requires opening of breathing circuit. This can cause the loss of the positive end-expiratory pressure of the patient. The position of the nebulizer in the breathing circuit is dependent on the nebulizer type or setup used for treatment. Different positions are discussed in Chapter 4.2.1 and the positions used with different nebulization setups are presented in following chapters. All current nebulizers require to be positioned vertically in order to function and the breathing circuit needs to be

positioned so that condensate fluid drains away from the patient. According to an interviewed nurse (Appendix 1, discussion 8), acquiring these settings requires effort and imaginative solutions from the clinician, because the position of the nebulizer needs to be optimized.

After the nebulizer is positioned in the breathing circuit, the next step is to add the medication in the drug chamber of the nebulizer. This is done after the positioning, in order to avoid the pouring of medication in the breathing circuit due to movement of the nebulizer. The medication is added through the filler port in the nebulizer with a syringe or with a pre-filled ampoule, as presented in Figure 6-2. The final step in preparing the nebulization equipment is to provide the driving force for nebulizer, either from the ventilator or from a stand-alone control module.

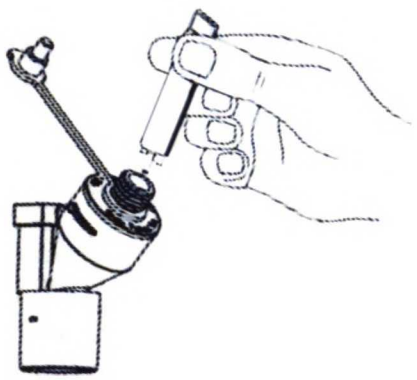

Figure 6-2. Example of adding the medication to the nebulizer's drug chamber with pre-filled ampoule. (Aerogen Inc., 2012)

After the equipment for nebulization is prepared, also the patient is prepared for nebulization. An interviewed nurse (Appendix 1, discussion 8) indicated that the preferred position for nebulization is supine, semi-erect or sitting, which is genuinely already acquired through positioning for ventilation. However, there is a limited amount of evidence for the effect of the patient position during the nebulization treatment. In addition to the positioning of the patient, additional mucus and secretions in airways can be removed by performing suction.

Third step of the workflow of nebulization treatment for ventilated patients is the preparation of the ventilator and the breathing circuit for the treatment process. The gas measurement sample line or sensor is recommended to be de-attached from the breathing circuit. With side-side stream gas measurement, where gas is sampled to the measurement unit, there is a risk of damaging the measurement unit, if the nebulized

medication is sampled in to the unit. Also the mode of ventilation is adjusted suitable for nebulization treatment.

When the preparations are completed the delivery of medication can be started. Generally the clinician needs to choose the length of the nebulization cycle, which is related to the dose delivered and the type of the nebulizer. During the administration of the medication the following of the condition of the patient is dependent on the severity of patient's pulmonary status. An interviewed nurse (Appendix 1, interview 1) suggested that it is uncommon that patient requires additional attention. If the dosage of the medication is larger than the capacity of the nebulizer unit, additional medication needs to be added during nebulization. Usually this requires interrupting of the nebulization treatment, but in the newest nebulizers additional medication can be added without interrupting the nebulization.

When the medication is delivered from the nebulizer, the nebulization treatment can be finished. First step is to remove the nebulizer unit from the breathing circuit. This is reverse process from the preparations. Though, if the patient is scheduled to have another nebulization treatment in a short period of time, the breathing circuit connecter can be left in place. An interviewed doctor (Appendix 1, interview 16) stated that this should not have any effect on the ventilation or the infection control of the patient. When the nebulizer unit is detached, the gas measurement can be reconnected to the breathing circuit and the ventilation settings return to original level.

Currently there are fully disposable pneumatic nebulizers which can be wasted after nebulization. Ultrasonic and vibrating nebulizers with advanced technology are generally more expensive and have reusable parts, which require cleaning and sterilization before they can be reused. According to an interviewed nurse (Appendix 1, discussion 8), this cleaning is performed by the clinician and takes five to ten minutes.

6.2. Setups for nebulization with mechanical ventilation

There are several companies providing different brands of pneumatic nebulizers and ultrasonic nebulizers suitable with mechanically ventilated patients, but there is only one brand of vibrating mesh nebulizer. Different setups related to the type of the nebulizer are discussed in this chapter.

6.2.1. Setup with the pneumatic nebulizer

The components required for setups with a pneumatic nebulizer are the pneumatic nebulization device, an adapter to connect the nebulization device in the breathing circuit, and a line for external gas source. The arrangement of these components is presented in Figure 6-3.

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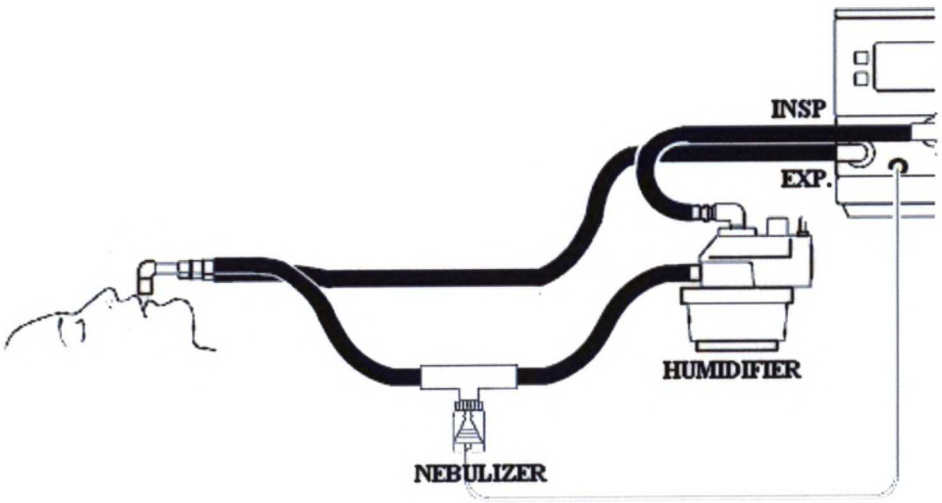

Figure 6-3. Setup for nebulization of mechanically ventilated patient with pneumatic nebulizer.

The nebulization device in this setup is a pneumatic nebulizer, whose operating principle is discussed in Chapter 3.6.3. Both single-use ad re-use pneumatic nebulizers are available for in-hospital settings. Usually the single-use nebulizers consist from one disposable component, which is wasted between every treatment. In comparison, the re-use nebulizer consists from two components, which are disposable drug chamber and reusable nebulization unit. Nebulization unit is generally washed between patients or treatments, but can be used for three to twelve months.

A pneumatic nebulizer is connected to the breathing circuit with a T-piece adapter. This adapter is usually proprietary for each brand. The placement of the connector is usually in the inspiration limb of the breathing circuit, between the patient and possible humidifier. An interviewed nurse (Appendix 1, discussion 8) pointed out that there are no guidelines or protocols recommending correct positioning, even though some brands recommend positioning to six inch from the y-adapter. The nebulizer also needs to be positioned vertically in upside position under the hoses, as presented in Figure 6-4. This positioning is required due to the operating principle of pneumatic nebulizers.

Figure 6-4. The connection and positioning of pneumatic nebulizer to the breathing circuit.

A pneumatic nebulizer requires gas flow to operate, and this gas flow is provided through a gas line, which is connected between the nebulizer unit and a ventilator. Almost all modern life support ventilators have built-in compressor for the gas flow required by pneumatic nebulizers. In the absence of this connection outer compressor is needed. With outer compressor there are minimal possibilities to achieve synchronization between the ventilator and the nebulizer.

6.2.2. Setup with the ultrasonic nebulizer

The setup with an ultrasonic nebulizer does not differ much from the setup with pneumatic nebulizer. The components needed are the ultrasonic nebulization device, an adapter to connect the nebulization device to the breathing circuit, and a connection between the ventilator and the nebulizer. The arrangement of these components is presented in Figure 6-5.

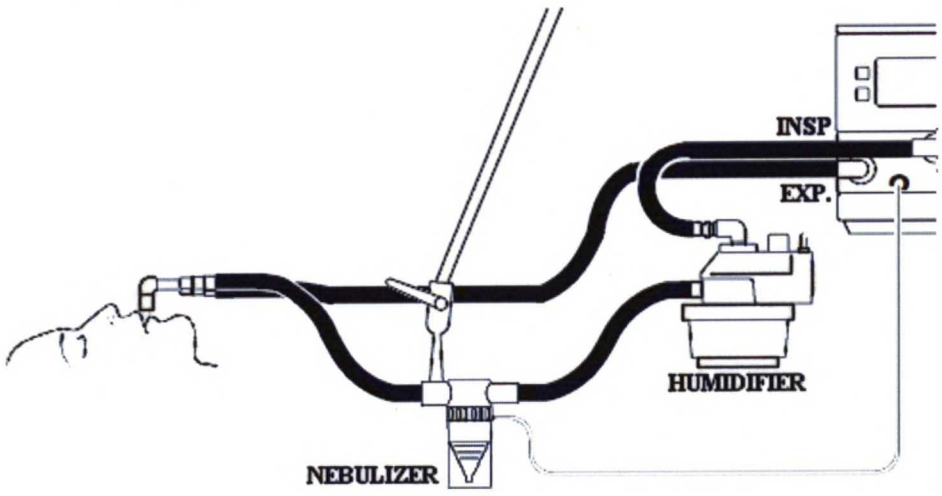

Figure 6-5. Setup for nebulization of mechanically ventilated patient with ultrasonic nebulizer.

The operating principle of ultrasonic nebulizers is discussed in Chapter 3.6.4. Ultrasonic nebulizers used for ventilated patients consist of two components: a disposable drug chamber and a reusable nebulization unit. Similar to re-use pneumatic nebulizers the nebulization unit is generally washed between patients or treatments.

Also, the connection method and positioning of ultrasonic nebulizers are similar to pneumatic nebulizers. One major difference between ultrasonic nebulizers and pneumatic nebulizers are the heavier weight of ultrasonic nebulizers. The ultrasonic nebulizer needs to be supported, in order to avoid the bending of hoses of the breathing circuit or even the binding of an endotracheal tube. According to an interviewed neonatal nurse (Appendix 1, interview 23) this is a major challenge with small patients with more fragile airways. The support for nebulizer units can be attained with a hanger in the connection adapter, with s supporting platform, or with a creative binding of hoses. The positioning of an ultrasonic nebulizer with the support of a hanger is presented in Figure 6-6. In addition, ultrasonic nebulizers tend to warm up, and are for this reason not recommended to be placed near the patient.

Figure 6-6. The connection and positioning of ultrasonic nebulizer to the breathing circuit.

Ultrasonic nebulizers need power from ventilator in order to operate. According to the interviewed product manager (Appendix 1, discussion 6), several of the modern day ventilators have an integrated power source for ultrasonic nebulizer, and this integration provides a possibility to synchronized nebulization treatment.

6.2.3. **Setup with the vibrating mesh nebulizer**

The components for the setup with the vibrating mesh nebulizer are the nebulization device, a connection adapter, and an external control unit. The arrangement of these components in ventilation care station is presented in Figure 6-7.

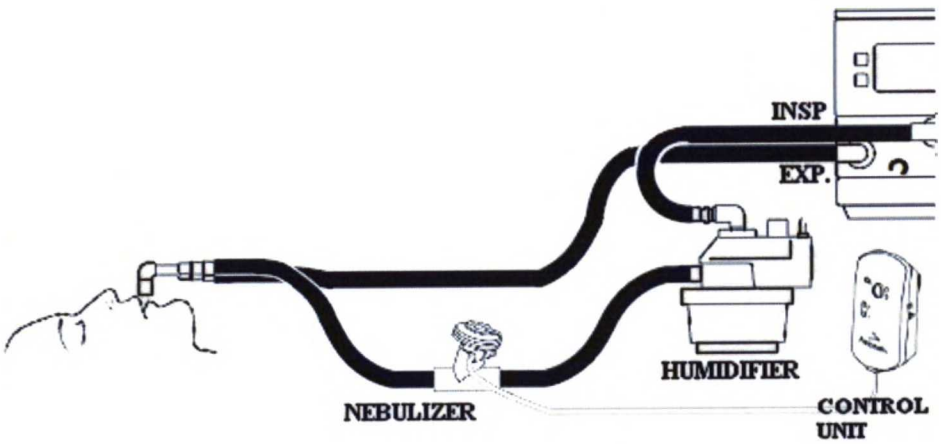

Figure 6-7. Setup for nebulization of mechanically ventilated patient with pneumatic nebulizer.

The vibrating mesh nebulizer in this setup consists of a reusable nebulization unit and a disposable drug chamber. The disposable drug chamber has a filling port, which can even be used to add additional medication during the treatment. During interviews a nurse (Appendix 1, interview 3) provided information that generally the reusable component of nebulization units is recommended to be cleaned between patients and replaced every twelve months. In this setup, the nebulization unit is connected to the breathing circuit with proprietary adapter, which can be left in to the circuit between treatments.

The operating principle of vibrating mesh nebulizer is discussed in Chapter 3.6.6. Because of the operating principle, the nebulizer needs to be positioned vertically upwards from the hoses, as presented in Figure 6-8. An interviewed nurse (Appendix 1, interview 3) noted that because of the low weight and the small size, the vibrating mesh nebulizer does not affect the hoses of an adult breathing circuit or the endotracheal tube. However, an interviewed neonatal nurse (Appendix 1, interview 23) expressed that with neonatal patients this supporting of the nebulization unit is still recommended.

Figure 6-8. The connection and positioning of pneumatic nebulizer to breathing circuit.

The most common vibrating mesh nebulization setup has an external control unit, but in the latest ventilator care stations this control unit is built-in to the ventilator. The control unit is used to adjust the length of the nebulization treatment. The vibrating mesh nebulizer is suitable also for synchronization with nebulizer and ventilator.

6.3. Nebulization therapy with mechanical ventilation

The interviews had also fixed questions, as presented in Appendix 2. Answers of the interviewees for these questions are combined in this chapter in order to generate statistical data.

6.3.1. The administration behavior with the nebulization treatment

The interviewees were asked to estimate the rate of patients receiving mechanical ventilation in their hospital unit. Based on answers of interviewees, from sixty to eighty percent of patients are mechanically ventilated during their stay in these high-acuity hospital units. Nebulization treatment is administrated from forty to sixty percent of these patients. In addition, from thirty-five to fifty-five percent of patients receive nebulization therapy during non-invasive ventilation. The estimations of use rates for nebulization during ventilation are presented in Table 6-1.

Table 6-1. The answers of Interviewees for questions of administration behavior with nebulization therapy.

Question	Average
Percent of patients mechanically ventilated	60 – 80 %
Percent of mechanically ventilated patients receiving the nebulization therapy	40 – 60 %
Percent of noninvasive ventilated patients receiving the nebulization therapy	35 – 55 %
General duration of the nebulization therapy in days	4 – 6 days
Average number of administrations per 24 hour	4 times
Average duration of a single drug administration with the nebulizer	8 – 13 minutes

The normal length of stay in intensive care units varies, but based on answers of interviewees the general duration of nebulization therapy is from four to six days. The administration of aerosolized medication is performed generally four times a day. The variation of the number of administrations depends on medications used. In some cases the number of administrations can be much higher, because some medications need to be administrated separately. The duration of single administration is dependent on the nebulizer type and dosage of the drug. But based on answers of interviewees, the average duration for a single drug administration is from eight to thirteen minutes.

As discussed in chapter 6.2, there are different setups for nebulization treatments. Based on answers of interviewees the use rate of these setups is presented in Table 6-2. Pneumatic nebulizers are used almost in half of the care stations, when setups with vibrating mesh nebulizer are used in thirty percent of care stations. Ultrasonic nebulizers are the least selected setup with use rate of twenty-four percent.

Table 6-2. Answers of interviewees on nebulizer setups for mechanically ventilated patients.

Nebulization setup	**Use rate**
Disposable Pneumatic nebulizer	34 %
Reusable Pneumatic nebulizer	12 %
Vibrating mesh nebulizer	30 %
Ultrasonic Nebulizer	24 %

6.3.2. **Challenges of clinician in nebulization therapy**

The overview of the work flow in the administration of nebulization treatment is discussed in Chapter 6.1. The interviewees were asked to recognize and prioritize the three most challenging work steps in the work flow of administrating nebulization therapy. These answers are presented in Table 6-3.

Table 6-3. The answers of interviewees on prioritizing challenges of nebulization therapy work flow.

Work Step	**Combined priorization**	**Number of clinicians prioritizing this challenge in corresponding position**		
		Highest challenge	Second highest challenge	Third highest challenge
Attaching the nebulizer unit to the breathing circuit	58 points	11	10	5
Holding the drug chamber of the nebulizer in the correct position	47 points	10	6	5
Cleaning the nebulizer after the therapy	25 points	3	5	6
Evaluating the efficiency of the drug delivery	15 points	1	4	4
Evaluating the condition of the patient during the therapy	8 points	1	1	3
Starting the nebulization treatment	6 points	0	1	4
	1st highest challenge = 3 points 2nd highest challenge = 2 points 3rd highest challenge = 1 points			

Two work steps were clearly raised above others by the interviewees. Firstly, attaching the nebulizer to the patient's breathing circuit was recognized as the most challenging work step. Secondly, positioning the nebulizer correctly was recognized as the second most challenging work step. These work steps were prioritized almost double as challenging work steps compared to the other work steps. Most of current nebulization devices contain reusable parts, which require cleaning after the administration. Cleaning the nebulizer was recognized as the third most challenging work step, prioritized clearly higher than other work steps beneath it.

In order to evaluate different features of nebulizers and nebulization setups, the interviewees were asked the challenges related to nebulization therapy. Furthermore, interviewees were asked to prioritize the recognized challenges. These challenges and the priorities are presented in Table 6-4.

Table 6-4. The answers of interviewees on prioritizing challenges related to nebulization therapy.

Challenge	**Combined priorization**	**Number of clinicians prioritizing this challenge in corresponding position**		
		Highest challenge	Second highest challenge	Third highest challenge
Attaching the nebulizer to the breathing circuit	43 points	9	7	2
Ensuring the efficiency of the drug delivery	24 points	6	2	2
Preventing the nebulized drug from tarnishing the breathing circuit, the ventilator or the gas monitor	20 points	2	7	0
Losing the patient's positive end-expiratory pressure	18 points	4	1	4
Maintaining the correct position of the drug chamber	16 points	3	1	5
Cleaning the equipment after the nebulization therapy	8 points	0	2	4
Limited amount of validations for the safety use of drugs	8 points	1	2	1
The extra bias flow from the nebulizer	5 points	0	2	1
Challenges to synchronize the nebulization to the ventilation	2 points	0	0	2
	1st highest challenge = 3 points 2nd highest challenge = 2 points 3rd highest challenge = 1 points			

Attaching the nebulizer unit to the breathing circuit is clearly recognized as the highest challenge in nebulization therapy. Loosing patient's positive end-expiratory pressure, which was recognized as the fourth highest challenge, is usually strongly linked to the challenge of attaching the nebulizer to the breathing circuit. Ensuring justified drug delivery was recognized as the second highest challenge, even though there currently are extremely limited amount of methods to actually evaluate the efficiency of nebulization treatment.

In nebulization treatment the goal is to deliver the aerosolized drug to the breathing circuit and with assistance of inspiratory gas flow to the patient lungs. However, as the aerosolized drug is mixed in the gas flow it tends to end up in the same places where gas flow moves in normal conditions in the breathing circuit. This tarnishing the

breathing circuit, the ventilator or the gas monitors was recognized as the third important challenge.

Interviewees also recognized two highly work step-related challenges, which were maintaining drug chamber positioning and cleaning equipment after nebulization. The two lowest prioritized challenges were related to different nebulizer types and their co-operation with ventilators, as extra bias flow is related to pneumatic nebulizers and synchronization is related to the communication between the nebulizer and the ventilator.

6.3.3. **Drugs used in the nebulization therapy**

The drugs used for nebulization therapy in their unit were asked from each of interviewees. The drugs, or brands, from answers of interviewees were then categorized based on the categorization presented in Chapter 4.3. The estimated percent of hospital units using each medication are listed in Table 6-5. In addition, drug formulations from answers of interviewees are presented for each medication. Based on answers, bronchodilators and corticosteroids are the most commonly used medications for ventilated patients with mechanical ventilation.

Table 6-5. Answers of interviewees on drugs commonly nebulized for mechanically ventilated patients.

Medication	Rate of Use	Drug formulations
Bronchodilators	93 %	β2-agonists Short-acting (3~6hr) Salbutamol / Albuterol Terbutaline Fenoterol Long-acting (>12hr) Salmeterol Formoterol Anticholinergic bronchodilator Ipatrobium bromide Magnesium sulphate
Corticosteroids	67 %	Budesonide Fluticasone
Antibiotics	26 %	Aminoglycosides: Amikacin, Tobramycin Colistin Polymyxins Vancomycin
Mucoactive drugs	15 %	Hypertonic saline Acetylcystaine Glucocorticosteroids, anticholinergics Surfactants
Vasodilators	4 %	Prostacyclins Nitric oxide

7. Analysis

Marketing research provides information for assessing the factors which are important for the customer. In this chapter the information from interviews is analyzed to generate the features that customer values in setups for nebulization with mechanical ventilation. Then the information from the literature review and from interviews is combined to evaluate different setups. At the end of this chapter, all this information is used for the opportunity and issue analysis of the setup of the case company.

7.1. Features of setups for nebulization therapy

This chapter is presenting features of nebulization setups that customer could value, which can also be referred to as customer needs. These features or customer needs are generalized from the customer challenges recognized in interviews, presented in Chapter 6. In addition, the reasoning for each of these features is discussed based the results from the interviews.

Unfortunately customers are not always clear to impress their needs, and because of that it is not always simple to recognize the features the customer values. Recognizing customer needs is challenging especially with new technologies, as customers are often unable to recognize features that do not yet existing features. The interviewed business development manager (Appendix 1, discussion 4) provided one method to tackle this challenge by starting from challenges the customers are facing.

These challenges can then be used as product features. For this reason, interviewees were asked to recognize major challenges in nebulization therapy and in the work flow of nebulization therapy. These challenges are presented in Table 6-4 and Table 6-3 respectively. Answers of interviewees were used to generalize the major features that customers would value in the setup for nebulization therapy. These features are presented in Table 7-1. Furthermore, these features are categorized under four different categories: Easy to Use, Quality of Care, Access and Cost of Care. This categorization was done in order to help recognizing the trends in customer needs.

Table 7-1. Features that customer values for nebulization setups of ventilated patients.

Feature	Category
Attaching method to the breathing circuit	Easy to Use
Cleaning of equipment	
Holding the nebulizer positioning	
Maintaining the cleanliness of the ventilation care station	
Efficiency of the drug delivery to the patient	Quality of Care
Maintaining the patients positive end-expiratory pressure	
Avoiding the extra flow caused by the nebulization treatment	
Available drugs to be used	Access of Care
Size & weight of the nebulizer	
Maintaining the positive end-expiratory pressure of the patient	
Efficiency of the drug delivery to the patient	
The dosage of the drug needed for a single treatment	Cost of Care
Efficiency of the drug delivery to the patient	
Workflow required for the treatment	

7.1.1. Features related to the Easy to Use -category

Easy to use -category presents features that simplify the work flow of nebulization therapy. Inside the Easy to use category, there are four different features of nebulization setup recognized: Attaching method of the nebulizer to the breathing circuit, cleaning of equipment, holding the nebulizer positioning, and maintaining the cleanliness of the ventilation care station.

The attaching method describes the technical solution for connecting the nebulization unit to the breathing circuit. This usually requires opening the breathing circuit in order to add additional adapter in hoses of the breathing circuit. In addition, the current nebulization devices require vertical positioning in order to operate. Interviewed nurses (Appendix 1, interviews 1,3,23,24,25 and 26) recognized that achieving the vertical positioning requires much effort and imagination from the clinician as the hoses of the breathing circuit tend to cause tilting of the nebulizer.

Most of current nebulization devices used in-hospital settings contain reusable parts, which require cleaning before re-use. An interviewed nurse (Appendix 1, interviews 1 and 8) listed that the options for the cleaning are hand washing, machine washing, disinfection with suitable disinfectants, or steam autoclaving. Regardless of the method, the clinicians usually perform the cleaning process. The main challenge in cleaning of nebulization equipment is mainly the time and effort it requires rather than the difficulty of the cleaning.

In nebulization treatment the goal is to deliver the aerosolized drug to the breathing circuit and with the assistance of inspiratory gas flow to the lungs. However, as the aerosolized drug is mixed in the gas flow, the drug tends to follow the gas flow in breathing circuit. The interviewed principal engineer (Appendix 1, discussion 2) noted that the aerosolized drug might end up in the expiratory limb of the breathing circuit or the gas monitoring lines.

This not only reduces the efficiency of nebulization treatment, but can damage the equipment where gas flows. The equipment under the risk are ventilator or gas measurement unit. The severe hazards for the ventilator can be avoided with a filter in an expiratory limb of the breathing circuit and for gas monitor by removing the gas measurement connection for the duration of nebulization. Regardless, the aerosolized drug might still tarnish the breathing circuit. Ventilators do not usually have an in-built gas scavenging system, so the expired gas is released in to the room-air. An interviewed doctor (Appendix 1, interview 16) also recognized unwanted consequences with this, as clinicians are continuously exposed to drug.

7.1.2. **Features related to the Quality of Care -category**

Quality of Care can be seen as the clinical response of the patient to the treatment. Quality of Care -category presents features that have a clear effect on the patient condition and to the outcome of the therapy. Three features in this category are: efficiency of the drug delivery to the patient, maintaining the positive end-expiratory pressure of the patient, and avoiding the extra flow caused by the nebulization treatment.

Interviewed doctors (Appendix 1, interviews 16 and 23) indicated that currently there are no methods to evaluate the amount of drug deposited on the target site of the patient lungs. In-hospital settings the only method to evaluate the efficiency is to follow that the entire dosage of drug is aerosolized from nebulizer. Sometimes this amount of medication leaving the drug chamber can be recognized as efficiency. Even though, this amount reveals only the output rate of nebulizer not the actual efficiency of nebulization therapy. Interviewed doctor (Appendix 1, interview 16) described that the efficiency of nebulization therapy can be evaluated by following changes in the patient condition. Though, the changes on patient condition are not necessary instant, and for this reason the evaluating of efficiency through patient condition is highly delayed. For these

reasons, the clinicians do not have method to evaluate the actual efficiency of nebulization therapy at the moment.

Interviewed principal engineer (Appendix 1, discussion 2) indicated that currently the efficiency of nebulization can only be measured in laboratory settings with certain limitations. This efficiency is complex to evaluate, but it is finally determined by the percentage of drug delivered to targeted site. There are several factors affecting to the efficiency of drug delivery and these are already discussed in Chapter 4.2. Synchronization of aerosolization with inspiratory flow has a positive effect on the efficiency, but perfect synchronization with nebulizer and inspiratory flow is not easy to achieve. The goal in synchronization is to combine the aerosolized drug to the inspiratory flow in breathing circuit.

The connection method for the nebulizer to the breathing circuit also effects the patient condition. That is because according to an interviewed nurse (Appendix 1, discussion 8) the opening of patient breathing circuit is the main cause of losing the positive end-expiratory pressure of the patient. An interviewed doctor (Appendix 1, interview 23) recognized maintaining the PEEP as a key feature with patients with lower tidal volume or severe pulmonary disease. That is because PEEP keeps alveoli of the patient open and prevents the collapsing of the lungs.

Third feature in Quality of Care –category is the extra bias flow caused mainly by pneumatic nebulizer. The operating mechanism of pneumatic nebulizers requires inlet gas as driving force of the nebulization. Interviewed nurse (Appendix 1, discussion 8) recognized the challenges in acquiring the correct ventilation settings in order to compensate this extra bias flow.

7.1.3. **Features related to the Access of Care -category**

Access of Care -category presents features that allow nebulization treatment to provide better health for more people through accessing new patient groups, care areas or providing new treatments for diseases. Four features were recognized in this category: Available drugs to be used, size & weight of the nebulizer, maintaining the positive end-expiratory pressure of the patient and efficiency of the drug delivery to the patient.

The wider selection of drugs increases access either by providing drugs for new diseases, by providing already existing drugs in formulation suitable for nebulization, or by providing drugs suitable for treatment of new patients groups. According to interviewed pharmaceutical industry specialist (Appendix 1, interview 3) the nebulization device and technology are not the only limiting factor on drugs available. In addition, the regulatory approvals and treatment protocols dictate the availability and usage of drugs in aerosol therapy. All the available drugs are even harder to define, as there are currently limited amount of standards or guidelines providing recommendations for the use of nebulized drugs for ventilated patients.

The increase in efficiency of drug delivery may also provide access to treatment new patients group. An interviewed doctor (Appendix 1, interview 23) pointed out that some patients have precise drug dosage requirements. These requirements prevent the use of nebulization therapy, as the amount of drug eventually deposited in the patient lungs may vary. More reliable drug delivery might increase the use of nebulization therapy with these patients.

Loss of the positive end-expiratory pressure can affect the patient condition, especially with patients with low tidal volume or severe pulmonary disease. This might lead to description of intravenous administration of drugs instead of nebulization.

The nebulizer unit is additional equipment near the patient, and can even affect the positioning of other components in the breathing circuit. Also the smaller size of the nebulizer allows treating personnel to have better visibility and access to the patient. Heavy nebulizers might easily cause the bending of hoses of the breathing circuit. An interviewed doctor (Appendix, interview 23) recognized this as a major risk with patients with very fragile airways. For these reasons, the smaller size and weight of nebulizer unit might provide additional access to the perinatal care area.

7.1.4. **Features related to the Cost of Care -category**

Cost of Care -category presents features that effect the total cost produced by the treatment during the patient stay in hospital. The features in this category are: The dosage of the drug needed for a single treatment, efficiency of the drug delivery to the patient and workflow required for the treatment.

More efficient drug delivery increases the amount of drug deposited into patient lungs and can therefore have twofold influence in cost of care. Firstly, both of the interviewed doctors (Appendix 1, interviews 16 and 23) recognized the possibility that increased efficiency can increase the clinical outcome of the patient treatment. Increased clinical outcome reduces the length of stay in hospital, and the total cost of treatment. Secondly, the increase in the amount of the drug deposited to patient lungs allows same clinical outcomes with lower drug dosages. This allows direct savings in medication costs.

Workflow required for a single nebulization treatment directly influences the time that a clinician is not able to use for treating patients. The features in Easy to Use -category are heavily linked in reducing the workflow required for a single nebulization therapy, and this way affecting also to the Cost of Care –category. In addition,

Table 6-3 presents the work steps that clinicians recognized as most challenging in administrating nebulization therapy.

7.2. Evaluation of setups for nebulization with mechanical ventilation

In this chapter the different nebulization setups are evaluated base on the features discussed in Chapter 7. The evaluated three setups are presented in Chapter 6.2 and two setups based on the solution of the case company. The case company solutions can be divided into two setups, based on the connection method of the nebulizer to the breathing circuit. First setup is with an additional adapter to an inspiratory limb or between the y-piece and the endotracheal tube. This setup is similar to current setups with vibrating mesh nebulizers. In another setup, the nebulizer is connected with a designed y-piece, as presented in Figure 4-4.

The evaluation is done in the scale from one to five. In this scale the rating three presents the level of feature that is currently reachable without any notable efforts. Rating two describes situation that does not meet the currently acquirable level. Same time, rating one describes that features are clearly under the currently acquirable level and generates notable challenges compared to the acquirable level. If the setup provides clear improvement to the acquirable level, it receives rating five. Rating four is achieved in two situations. First, if the setup is able to reach rating five with minor adjustments. Second, if the setup has possibilities to improve the acquirable level, but there is not yet evidence available on this. The ratings for each setup are presented in Table 7-2.

Table 7-2. Evaluation of different nebulization setups based on features that customer values.

		Case company with designed y-piece	Case company with basic connector	Vibrating mesh Nebulizer	Ultrasonic nebulizer	Disposable Pneumatic nebulizer	Reusable Pneumatic nebulizer
Easy to Use	Attaching method to the breathing circuit	5	3	3	1	2	2
	Cleaning of equipment	3	3	3	2	5	2
	Holding the nebulizer positioning	5	5	3	2	2	2
	Maintaining the cleanliness of the ventilation care station	4	3	3	2	2	2
Quality of Care	Efficiency of the drug delivery to the patient	4	3	3	2	2	2
	Maintaining the patients positive end-expiratory pressure	4	1	1	1	1	1
	Avoiding the extra flow caused by the nebulization treatment	5	5	5	5	1	1
Access of Care	Available drugs to be used	4	4	4	3	2	2
	Size & weight of the nebulizer	5	5	3	1	3	2
	Maintaining the patient's positive end-expiratory pressure	4	1	1	1	1	1
	Efficiency of the drug delivery to the patient	4	3	3	2	2	2
Cost of Care	The dosage of the drug needed for a single treatment	4	4	4	3	1	1
	Workflow required for the treatment	5	4	3	2	2	3
	Efficiency of the drug delivery to the patient	4	3	3	2	2	2

1 = Clearly under the current acquirable level
2 = Does not meet the acquirable level currently
3 = The acquirable level currently
4 = Possibilities to increase the current situation, but need evidence / adjustments
5 = Improvement to the current situation

7.2.1. Evaluation of the Easy to Use -category

Current nebulization setups are connected to the breathing circuit with an additional adapter. This requires the opening and reconnection of the breathing circuit in order to place the connector. According to the interviewed clinicians (Appendix 1, interviews

1,2,3,16 and 23) this also effects conditions in the breathing circuit, and might require additional work to restore the conditions in the breathing circuit and the condition of the patient. In addition, the heavy weight of the ultrasonic nebulizer generates additional challenges in attachment, as ultrasonic nebulizer often requires external support.

Setup of the case company with designed y-piece completely skips the opening of the breathing circuit, as it is directly attached to the PEEP saver port. Also, the case company's setup with additional adapter simplifies this work step, as it would be similar to vibrating mesh nebulizer setups. In these setups the connection adapter can be left in the breathing circuit for the period between treatments. For these reasons, setups with ultrasonic nebulizers are rated lowest and the setup of the case company with designed y-piece is rated the highest.

Prober positioning of the nebulizer is important, because the operating principle of all current nebulizers requires vertical positioning to function and even minor tilt in position can increase the residual volume. Based on the opinions of the interviewed clinicians (Appendix 1, interviews 1,3,23,24,25 and 26) achieving the vertical positioning might require much effort and imagination, as the hoses of breathing circuits tend to cause tilting of the device. In contrast, the design of the drug chamber in the nebulizer of the case company makes the nebulizer position independent. For this reason, the setup of the case company is rated above other setups.

Cleaning of the components used in nebulization is usually done by the clinicians, and for this reason is feature in Easy to Use –category. Setups with disposable pneumatic nebulizers exceed all of the other setups, as all the components are wasted. Nebulizers in all the other setups consist from a reusable nebulizer unit and a disposable drug chamber. The cleaning of the nebulizer unit does not differ significantly between these nebulizer types, and for this reason setups are rated to be at the same level.

Maintaining the cleanliness of the ventilation care station is feature of Easy to Use – category, because drug in undesired parts of the breathing circuit can not only tarnish the breathing circuit but also cause hazards to the equipment of the care station. The cleanliness of ventilation care station is secured, if the undesired deposition is prevented. For this reason, the ability to maintain the cleanliness is also related to the efficiency of drug delivery. Both continuous nebulization and also position distal from the patient increases the amount of drug inside the breathing circuit. According to the interviewed principal engineer (Appendix 1, interview 2) the increased amount of drug in inspiratory limb correlates with the amount of drug ending in the expiratory limb of the breathing circuit during the expiration of the patient. This effect can also be reduced with synchronization of nebulization to inspiration flow of ventilator. Because of the possibility to synchronization, setups with vibrating mesh or ultrasonic nebulizers maintain the cleanliness better than setups with pneumatic nebulizers. In addition, the positioning near patient may prove to be beneficial in favor of the case company's setup with a designed y-piece.

7.2.2. Evaluation of the Quality of Care -category

Efficiency was recognized as one of the key features in Quality of Care –category. Currently there are no feasible methods to estimate the efficiency of nebulization treatment in normal hospital settings. Precise information from the amount of drug deposited in the target area could only be acquired either with tomograpchic imaging or setups with test lungs. Chapter 4.2 discusses on factors affecting the efficiency of nebulization therapy, and interviewed nurse (Appendix 1, discussion 8) confirmed that clinicians usually adjust these factors to optimize the outcome of nebulization treatment. It is notable that nebulization setups, presented in Chapter 6.2, affect several of these factors, and can be evaluated based on these.

The type of the nebulizer is one of the main factors affecting the efficiency, because the particle size generated by nebulizer affects the delivery site and amount of the drug deposited there. Vibrating mesh nebulizers generate more uniforms and smaller particles compared to ultrasonic nebulizers, which exceed pneumatic nebulizers in this feature. Also, the output rate of the nebulizer can shorten the treatment time and similarly increase the efficiency. Vibrating mesh nebulizers have a higher output rate than ultrasonic nebulizers and pneumatic nebulizers. For these reasons, the vibrating mesh nebulizers are more efficient than ultrasonic or pneumatic nebulizers.

Also the synchronization with nebulization and the inspiratory flow affects the efficiency. Pneumatic nebulizers can operate continuously or intermittently controlled by the gas source from ventilator, but still the ventilator synchronization is challenging to acquire. On the contrary, ultrasonic or vibrating mesh nebulizers are able to be synchronized with ventilator inspiration flow. This even emphasizes the higher efficiency of vibrating mesh nebulizers.

In the solution of the case company, the nebulizer is positioned near the airways of the patient. This reduces the distance that the drug needs to travel in the breathing circuit, and by this way limiting the possibility to have undesired deposition. Anyhow, there is still need for more evidence from the effect of this to the efficiency.

According to the interviewed doctors (Appendix 1, interviews 16 and 23), the opening of the breathing circuit is the main cause of losing the positive end-expiratory pressure of the patient. This in mind, the setup of the case company with designed y-piece provides possibility to prevent the loss of PEEP during the connecting of nebulizer. Though, interviewed nurse (Appendix 1, interview 3) acknowledged some tricks to try to overcome this challenge with current setups. Firstly, the additional adapter can be connected to the breathing circuit at the beginning of the ventilation treatment. Secondly, the endotracheal tube can be "closed" with clips to maintain the pressure in patient lung. But this affects the ventilator settings, and the interviewed product manager (Appendix 1, discussion 6) noted that this can cause extra flows after the release of the blockage.

More significant source of extra bias flow are the pneumatic nebulizers, as they reguire gas flow as driving force of operation. This gas flow also has a direct effect on the flow and pressure in patients breathing circuit. This challenge is not relevant with ultrasonic or vibrating mesh nebulizer, because different operating mechanism.

7.2.3. Evaluation of the Access of Care -category

The available drugs for different nebulization setups are mainly linked to the type of the nebulizer. Vibrating mesh nebulizers generate more uniforms and smaller particles compared to ultrasonic nebulizers and pneumatic nebulizers, and for this reason are suitable for broader selection of the drugs. In addition, the available drugs are highly related to the efficiency. Because some drugs require precise dosages, they cannot be used if there are uncertainties in the amount of the drug deposited to the target site.

The size and the weight of the nebulizer can affect the connecting and positioning in the breathing circuit, because heavy nebulizers can bend the hoses of the breathing circuit or large nebulizers can block the access to the patient. Pneumatic nebulizers and vibrating mesh nebulizer are comparable in size and weight, when large sized and heavier ultrasonic nebulizers cannot be positioned near the patient and they require external support in order not to bend the breathing circuit. In these matters, the solution of the case company over exceeds all other evaluated nebulizer setups.

7.2.4. Evaluation of the Cost of Care -category

The time that clinicians spend in setting up the setup for the nebulization is directly removed from time to complete other tasks. The workflow required for the nebulization is dependent on the setup, and effectiveness in the workflow is mainly linked to the Easy to Use –category. An interviewed doctor (Appendix 1, interview 23) noted that treatment guidelines might request certain treatment steps to be completed before nebulization, but these are most likely similar for all the setups.

According to an interviewed doctor (Appendix 1, interview 16) the dosage of the drug is based to secure the desired quantity of the drug at the target site. So obviously, evidence of more quantity of the drug delivered to the target site, would allow reducing the dose of the drug. In addition, the lower residual volume of the nebulizer would reduce the dose.

Because the features in Cost of Care –category are highly linked to features in other categories, the results of the evaluation between different setups are common with evaluation of other categories. Especially, increase in efficiency provides several cost reducing possibilities: reduced drug costs as result of reduced dosages, reduced treatment costs as result of reduced time of stay in hospital, and reduced future costs as

a result of a better clinical outcome of the treatment. Though, it should be noted that the cost of the nebulizer unit and it components effects the total cost of the care.

7.3. Opportunity and issue analysis

This chapter discuss about opportunities and issues for the setup of the case company. These are analyzed with the SWOT analysis method and based on the features that customers value, which are presented in Table 7-1. Results of this analysis are presented in the Table 7-3. In this analysis not all features are listed, but rather only features that are related to success factors.

Table 7-3. The SWOT matrix of the opportunity and issue analysis for the setups of the case company.

Strength	**Weaknesses**
• The connection method to reduces work steps in treatment • The connection method enables the maintaining of the PEEP of the patient. • The solution might increase the efficiency of the drug delivery. • Position free operation of the nebulizer	• Unproven placement of the nebulizer in the breathing circuit • Majority of benefits compared to setups with vibrating mesh nebulizers are based on the new placement • Cost of the vibrating mesh technology
Opportunities	**Threats**
• An easy connection to the breathing circuit is the highest prioritized in challenges for nebulization setups with mechanical ventilation. • The efficiency is key feature in high-level categories that customer values • The vibrating mesh technology allows varying the mesh hole size. This enables more uniform and smaller particles, and this way a broader availability of drugs. • Majority of current nebulization setups have features that make them unfeasible for perinatal care area.	• The proposed placement of the case company's nebulizer is currently not approved • To achieve effective synchronization collaboration with ventilators is required • Regulatory approval challenges with increased efficiency or with specific drugs

7.3.1. Opportunities for the setup of the case company

In the marketing research interviews connecting the nebulizer to the breathing circuit was clearly the highest prioritized challenge in nebulization therapy, and it was also recognized as a feature that customers values. Another highly recognized feature was efficiency of the drug delivery, which was feature in the Quality of Care- , Access of Care- and Cost of Care -category. These customer needs provide an opportunity to the setup of the case company, as it over exceeded setups with a pneumatic nebulizer and setups with an ultrasonic nebulizer in these features. This is even emphasized by the results that at the moment the vast majority of hospitals have either setup with a pneumatic nebulizer or setup with an ultrasonic nebulizer.

When the majority of hospital have setups with a pneumatic nebulizer or setups with an ultrasonic nebulizer, the more advantaged vibrating mesh technology of the case company provides additional opportunities. The more uniform and smaller particles generated by vibrating mesh technology are, more compatibility to a broader selection of drugs is provided. In addition, the increased efficiency expands the selection of drugs available.

In perinatal care area the requirements for nebulizers are more demanding, as according to interviewed doctor (Appendix 1, interview 23) neonatal patients with lower tidal volumes and more fragile respiratory systems require individualized dosages precisely delivered. This emphasizes the features related to the Access of Care –category, where the setup of the case company has benefits over current setups. The advantages are result of the smaller size and the lighter weight of the nebulizer unit, and the possible increase in the efficiency.

7.3.2. Threats for the setup of the case company

Majority of the recognized strengths for the setup of the case company are related to the placement of the nebulizer unit. This also generates one threat for the setup of the case company, as this placement is currently not approved in the markets. The case company would need to have evidence of the benefits of this placement in comparison to the current practices.

One requirement for the suitability of the new placement is effective synchronization with ventilators, as based on the already existing evidence new placement is ineffective without synchronization. To secure functional synchronization it is almost required that the control unit of the nebulizer unit is built-in to the ventilator. This produces another threat for the setup of the case company, as the effective collaboration with ventilator manufacturers needs to be achieved.

The increased efficiency of the drug delivery with the setup of the case company might cause challenges in regulatory approval. There is a risk of accidental overdosage of the

drug, because the dosage requirements are reduced compared to current practices. One possibility to tackle this challenge is the use of prefilled drug chamber, because then there are no changes in workflow of nebulization treatment. Unfortunately, this solution causes two new threats. Firstly, the case company is partially dependable on their ability to enter into collaborative relationship with partners to commercialize the prefilled drug chambers from all of the drugs required in-hospital. Secondly, according to an interviewed regulatory specialist (Appendix 1, discussion 10) the combination of a new nebulizer and a prefilled drug chamber might be required to file regulatory approvals through New Drug Application regulations, which requires time consuming clinical trials to demonstrate the safety of the drug.

7.3.3. Strengths of the setup of the case company

The connection method through the PEEP saver port provides two strengths to the setup of the case company. This simple connection reduces work steps in preparation of the breathing circuit. In addition, the connection method of the case company enables maintaining the positive end-expiratory pressure, because there is no need to open the breathing circuit for attaching of the nebulizer.

The vibrating mesh technology used in the nebulizer of the case company has been proved to be more effective than the other nebulization technologies. These factors provide the setup of the case company a possibility to be more efficient than majority of the current nebulization setups. Also the placement of the nebulizer near the patient might increase the efficiency, as it reduces the distance that drugs needs to travel in breathing circuit. If the placement near the patient proves to be effective, the solution of the case company would be more efficient than any other of the current setups.

The fourth strength of the setup of the case company is the position free operation principle, which provides benefits. Firstly, it simplifies the work steps in treatment, because compared to other setup it does not require effort to maintain the vertical position. Secondly, the position free operation eliminates the residual volume caused by tilting of the nebulizer. Thirdly, it might provide access to care areas, where maintaining vertical positioning is not possible.

7.3.4. Weaknesses of the setup of the case company

Some uncertainties that can be seen as weaknesses are related to the placement of the nebulizer unit in the setup of the case company. First uncertainty is the placement to the y-piece, where the expiration and inspiration air flows, have in studies proved to be inefficient. First explanation for this is the pressurization of the expiratory limb during the inspiratory flow. Second is the nebulization during the expiratory flow, because insufficient synchronization of the nebulizer and the ventilator.

Another uncertainty related to the placement is the possible tarnishing of nebulization device by the secretions of the patients. The mechanical design of y-piece should be designed to prevent the nebulizer from these secretions in order to avoid the secretions preventing nebulizer from operating.

Third uncertainty is produced by the connection through the PEEP saver port, as according to interviewed nurse (Appendix 1, interview 2) there are occasionally patients, who need suction in the middle of the nebulization treatment, especially in neonatal patients with low tidal volume. Also, in order to allow closed suctions, the nebulizer should be removed from the PEEP saver port middle of the nebulization treatment.

If any of the uncertainties related to the unproven position causes the defunctionality of this placement, the breathing circuit connection in the setup of the case company would be similar to the current setups with a vibrating nebulizer. In this case, the setup of the case company would be as efficient as current setups with vibrating nebulizer.

Another weakness of the case company's setup is the price of the nebulizer. Because of the mesh plate in vibrating mesh technology, the vibrating mesh nebulizers are more expensive than pneumatic nebulizers. For this reason, the purchase cost of the setup of case company would be multi-fold compared to setups with pneumatic nebulizers. Though, there are possibilities to prove reduces in the total cost of care.

PART IV: DISCUSSION & CONCLUSION

8. Discussion & Conclusion

The purpose of this study was to analyze the current market situation of nebulization with invasive mechanical ventilation. The study concentrated on understanding the current theoretical background of aerosol therapy for ventilated patients, identifying current practices of aerosol therapy for ventilated patients in-hospital settings and defining how current practices can meet the customer needs for nebulization with mechanically ventilated patients.

In this study it was obtained that the understanding of human pulmonary physiology has provided possibility for targeted drug delivery with minimum systematic effects. This has aided the increase of aerosol therapy as treatment of respiratory diseases. In addition, inhalation as a route of administration has also increased as a result of more reliable and efficient vibrating mesh nebulization technique.

Adequate background knowledge of the various elements effecting the nebulization treatment, serves as the basis for identifying opportunities to satisfy unfulfilled customer needs. For this reason, medicines used with the nebulization and the factors affecting the efficiency of nebulization with ventilation was recognized and analyzed. The selection of medications currently used in-hospital with nebulization is broad, consisting of bronchodilators, corticosteroids, antibiotics, mucoactive drugs and vasodilators. The use rate of these differs between communities, but bronchodilators are administered to nearly every ventilated patient.

The current practices in hospitals were investigated and typical setups for nebulization with mechanical ventilation were identified. Identifying the current practices, have proved that there is a change in progress. There clearly exists a traditional solution with less efficient pneumatic nebulizer, which the new more efficient solution with vibrating mesh nebulizer is challenging. The advantages of vibrating mesh nebulizer are so major, that it still requires adaptation from professional community to be able to take full advantage of it capabilities.

To understand the customer needs, medical professionals were interviewed and asked to recognize the major challenges in nebulization therapy with mechanical ventilation.. Based on these answers major features valued in nebulizer setups for ventilated patients could be recognized. These features were related to either ease the workflow of the clinician, to increase the quality of the therapy, to allow an access to treat earlier untreated patient populations, or decrease the total cost of the treatment. The case company solution was then compared to the competitive solutions in these features.

Based on this, competitive advantages for the case company's nebulizer solution were recognized. The major ones compared to the current competing vibrating mesh setups

were the position free operation of the nebulizer unit and possibility for increased delivery as a result of new placement of the nebulizer unit. In addition, the case company's solution over exceed the traditional setups in several other features, for example in more simple connection method to the breathing circuit and in maintaining the positive end-expiratory pressure during the treatment. These features increase the competitive advantage especially in the perinatal care area.

Though, there were also recognized challenges to resolve, that if left unresolved could limit the market potential of the case company's nebulizer solution. First of the challenges is the compatibility with noninvasive ventilation or compatibility to invasive ventilation with breathing circuits with a general branching unit. Another one is the unproven placement of the nebulizer unit, which needs clinical evidence to support this change of earlier practicalities. In addition, the inability to form beneficial collaboration with pharmaceutical companies could affect the case company's capability to use prefilled drug chambers with their solution.

The quality of this study can be evaluated by the reliability and validity. Reliability of the study is considered good for the scope of the study. The data collection was planned carefully in advance. In this study the data collection method presented in Figure 5-1 acted as study protocol. The data from interviews and from meetings were archived to the study database afterwards. Additionally, notes and documents from secondary sources were archived to the database. Due to several sources of data in this study, the data is cross-checked before included in this study. To secure the validity, the interview themes, structures, and questions were defined before interviews. Also, the data in this study was analyzed with several different methods. Finally the key stakeholders in the case company reviewed the results and agreed with the findings of the study.

Within the quality of the study the weakest link is its focus in high-acuity intensive care units, which lowers the reliability of the study outside of the scope. This limits the generality of finding and recommendations to only for high-acuity intensive care units. However, it has to be taken into account that in the absence of other studies this research provides new founding also outside high-acuity intensive care units. The collected literature theory and the careful documentation of the data collection procedure allow the easy and accurate replication of the study. The validity of this study can be questioned, as the macro-environmental factors were not in the scope of the study. Even though the economic factors affect the business potential of a product, their direct effect on the situation at the market is questionable.

PART V: REFERENCES AND APPENDICES

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Appendices

Appendix 1. Interviews and discussions.

	Type	Interviewee	Industry / Care area	Date
Pre-research discussions	Discussion 1	Principal Engineer	Medical Device Industry	22.8.2011
	Discussion 2	Principal Engineer	Medical Device Industry	25.8.2011
	Discussion 3	Product Manager	Pharmaceutical Industry	20.10.2011
	Discussion 4	General Manager	Business Development, Medical Device Industry	26.10.2011
	Discussion 5	Product Manager	Medical Device Industry	14.10.2011
	Discussion 6	Product Manager	Medical Device Industry	4.11.2011
	Discussion 7	Clinical Research Manager	Medical Device Industry	13.10.2011
	Discussion 8	Nurse	Intensive Care Unit	20.10.2011
Market-research interviews	Interview 1	Nurse	Intensive Care Unit	4.11.2011
	Interview 2	Nurse	Neonatal ICU	3.11.2011
	Interview 3	Nurse	Intensive Care Unit	21.11.2011
	Interview 4	Nurse	Intensive Care Unit	22.11.2011
	Interview 5	Nurse	Intensive Care Unit	22.11.2011
	Interview 6	Nurse	Operating Room	22.11.2011
	Interview 7	Doctor	Neonatal ICU	22.11.2011
	Interview 8	Nurse	Intensive Care Unit	23.11.2011
	Interview 9	Nurse	Intensive Care Unit	23.11.2011
	Interview 10	Nurse	Intensive Care Unit	23.11.2011
	Interview 11	Respiratory Therapist	Intensive Care Unit	24.11.2011
	Interview 12	Respiratory Therapist	Operating Room	24.11.2011
	Interview 13	Respiratory Therapist	Neonatal ICU	24.11.2011
	Interview 14	Nurse	Intensive Care Unit	25.11.2011
	Interview 15	Respiratory Therapist	Intensive Care Unit	25.11.2011
	Interview 16	Doctor	Intensive Care Unit	29.11.2011
	Interview 17	Nurse	Intensive Care Unit	29.11.2011
	Interview 18	Nurse	Intensive Care Unit	29.11.2011
	Interview 19	Nurse	Intensive Care Unit	29.11.2011
	Interview 20	Nurse	Intensive Care Unit	30.11.2011
	Interview 21	Respiratory Therapist	Intensive Care Unit	1.12.2011
	Interview 22	Respiratory Therapist	Intensive Care Unit	1.12.2011
	Interview 23	Doctor	Neonatal ICU	7.12.2011
	Interview 24	Nurse	Neonatal ICU	7.12.2011
	Interview 25	Nurse	Neonatal ICU	7.12.2011
	Interview 26	Nurse	Neonatal ICU	7.12.2011
	Interview 27	Respiratory Therapist	Intensive Care Unit	8.12.2011
Evaluative discussions	Discussion 9	Principal Engineer	Medical Device Industry	23.11.2011
	Discussion 10	Regulatory Affairs Leader	Medical Device Industry	22.2.2012
	Discussion 11	Product Manager	Medical Device Industry	6.5.2012

Appendix 2. Interview structure.

Background information of interviewed clinician.

1. In what care area you work?
2. What is your primary position?

Current state of nebulization therapy in-hospital.

3. What percent of patients receive mechanical ventilation in your unit? Invasive/non-invasive?

   0 – 20 % / 20 – 40 % / 40 – 60 % / 60 – 80 % / 80 – 100 %

4. What percent of patients with invasive ventilation receive a nebulization treatment?

   0 – 20 % / 20 – 40 % / 40 – 60 % / 60 – 80 % / 80 – 100 %

5. What percent of patients with non-invasive ventilation receive a nebulization treatment?

   0 – 20 % / 20 – 40 % / 40 – 60 % / 60 – 80 % / 80 – 100 %

Administration of nebulization therapy.

6. How is the nebulization therapy of ventilated patient performed in-hospital currently (Work Steps)?

7. What equipment are needed for administration of nebulization therapy?

8. What are in priority order the five most challenging work steps in nebulization of ventilated patients?

9. How often is nebulization therapy administrated and for how long?
   - Duration of therapy in days?
   - Number of administrations per 24 hour?
   - Duration of single drug administration?

10. How many minute's time is spent in one nebulization treatment? (ex. half an hour with 2 nurses = 1 hour nurse labor)

Personal opinions of nebulization therapy.

11. What in your opinion are in the priority order the three major benefits of nebulization therapy?

12. What in your opinion are in the priority order the three major challenges administrating a nebulized drug in your unit?

Medications used in nebulization therapy.

13. What are the most common nebulized drugs for ventilated patients in your unit? What are the dosages?